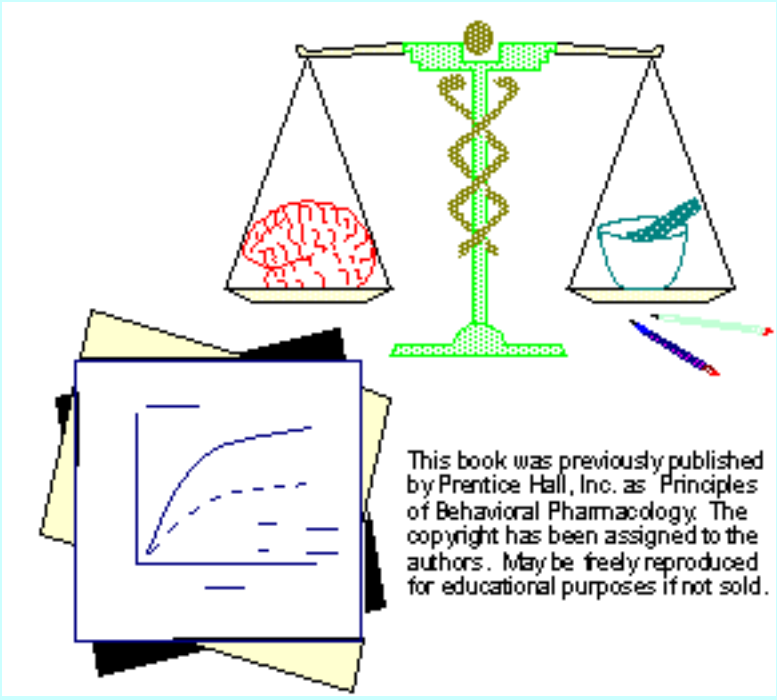
Drugs, Brains and Behavior

by

C. Robin Timmons & Leonard W. Hamilton



Available on the web both at Rutgers University and at Drew University.
Also available as a 2.2 MB .pdf file: dbb.pdf

Notice

BIOGRAPHICAL INFORMATION

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Related Materials

The Making of Drugs, Brains and Behavior An article about the process of creating this electronic textbook.

Psychopharmacology A brief chapter that summarizes the history and general concepts of psychopharmacology.

Index of Drugs: A comprehensive listing of psychoactive drugs, cross indexed by generic names, trade names, and diagnostic categories for which the drugs are prescribed.

RUCS Newsletter
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Creating an Online Textbook

For Fun and Profit?

Actually, it is not all that much fun. And there is no profit. But the process of creating an online textbook does have its rewards, and *Newsletter* editor Susan Hagan asked us to write about our experiences in creating our online textbook entitled Drugs, Brains and Behavior (http://www.rci.rutgers.edu/~lwh/drugs/).

Most of the material that is included in the current iteration of this textbook was previously published in hard copy (Hamilton, L. W. & Timmons, C. R., *Principles of Behavioral Pharmacology*, Englewood Cliffs, NJ: Prentice-Hall, 1990). Our recollection is that creating this textbook in traditional format was not all fun and profit either.

After the text went out of print, we began to entertain the idea of transferring it in an online format. But first, we had to go through the somewhat lengthy process of getting the copyrights assigned back to the authors. There was nothing especially complex about this, but it took several months to work through the corporate structure and find the person who could do this. Fortunately, we had created virtually all of the original artwork ourselves, so we did not face the daunting task of going back to a long list of publishers and authors for new permissions. For those of you who are currently planning to write a traditional textbook, you may want to consider writing something into your contract and permission requests to cover the possibility of future (or concurrent) electronic publishing rights.

Finally, the copyrights were in order, we had found the diskettes that held the original text files for the book, and had collected all of the graphics files for the artwork. We had a version of Corel WordPerfect© that includes simple procedures to translate documents into the file.htm format for the World Wide Web and an updated version of Lotus Freelance© that could add color and other features to our original line drawings. We had arranged our schedules for Thursdays at home to work on the project. Now, all we had to do was translate the files and upload them to the central computer and our project would be complete. Life was good.

The file for Chapter 1 was loaded into WordPerfect©, and with a few simple commands it was miraculously transformed from chap1.wpd into chap1.htm, and we excitedly loaded it into Netscape© to view it. It was probably 95 percent accurate, but cleaning up the remaining 5 percent was tedious. Once the document was cleaned up, there was still a lot of work to do. All of those italicized key words had to be linked to the glossary, the headings in the chapter outline at the beginning of the document had to be linked to the appropriate locations within the document, and the several dozen references in the chapter had to be linked to the appropriate citations in the bibliography. When we finally got good at it (this did not happen with chapter 1), this process, even with the use of numerous macros, required a full person day per chapter at the keyboard.

The links to the glossary and bibliography were still more complex because each of the several hundred entries had to be identified as a target so the text could be linked to it. These conversions of glossary and reference lists from word processor text into the appropriate file.htm formats were equivalent in workload to at least two or three chapters of text each. It was at this point that we began to realize that having all of the material already written was a mixed blessing--many of these formatting details can be handled very easily from the keyboard if they are done as the text is initially entered. (Did we mention that years ago when the original text was being put together, we had to translate the text files from Commodore to IBM because technology was progressing faster than we were writing?)

Now for the figures (requiring still more links in the text, of course), which had been created on Freelance©. We happen to like Freelance©, but the people at the aid station seemed a bit taken aback by the term, and as I recall, a crowd began to gather to have a look at this guy who was looking for this ancient piece of software in Windows© format. Ultimately, Drew University had a copy and we were overjoyed to see our figures brought to life with color in the new file.drw format. But, of course, the World Wide Web does not recognize this format, so we had to translate the files into something more compatible. Sometimes this conversion resulted in a fuzzy figure that lost all of its detail, other times it resulted in a figure that looked an awful lot like it had been drawn on an old computer, and it was always either too large or too small. By the time we figured out whether we should be converting the file.drw files into *file.jpg* or *file.gif*, and how to get them to look like they did on the original screen, we were ready to pull our *hair.out*! Once again, many of the problems of standard sizing, links, and so forth are easier if they are done as the artwork is being created.

Finally, there were the little details of figure captions (more links), a list of figure titles, easy links to the previous or next figure, and of course, a safety net so some unsuspecting reader would not get trapped in figure-land with no clear pathway back to the text.

Ultimately, we ended up with several hundred(!) files in file.htm, file.txt, file.gif format that included intricate links from text to figures to definitions to references to outside sources in a manner that seemed largely transparent to the user. Now we simply had to upload it onto the central system for access by anybody in the world. Oops! Not enough space.

When we contacted the central computer people who are in charge of space allocation and asked for an

increased allotment to put a textbook online, staff members at both universities (Drew and Rutgers) responded with the question that had already crept into our own minds: "Why would you want to do that?"

They happily agreed to increase our space allotments when we explained that the material could be easily accessed by our students from any computer terminal, that the cost to students for textbooks could be dramatically reduced, that the graphics were now readily available for classroom use in one of the new "smart" classrooms, that colleagues and students in other universities around the world would have access to the work, that it could be a "living" textbook with chapters being continuously updated, expanded, linked to other resources--yada yada. All of these arguments are beginning to sound a little trite, but they remain true.

We were up and running with an online text!

(As an example of how a reverse spin can be put on almost anything, we were approached by a textbook editor last week, via e-mail, to inquire if we wanted to publish this book in hard-copy.)

Several of our colleagues have visited the site and given us the socially appropriate "nice job", quickly followed by a mystified expression and the question, "But how do you make any money on this?" Our flip answer is that "We never made any money on the original hard copy!" Although not completely inured to a whiff of the pilf, we have (fortunately) never planned for our textbook writing to be a for-profit venture-- we view it as teaching.

When we finally reached the end of the project and had the textbook online, a whole bunch of Thursdays had passed by. There had been at least as many frustrations, pitfalls and delays as one encounters when working through a publisher to create a traditional hard-copy text. But both of us had independently reached the same conclusion and had found an unexpected reward: This is the very best work that we have done.

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PSYCHOPHARMACOLOGY

by

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FROM FOLK MEDICINE TO MODERN PHARMACOLOGY

The human experience is frequently characterized by our feelings toward certain aspects of our environment. We are frightened by things we do not understand, calmed by familiarity, anxious in the face of uncertainty, exhilarated by our accomplishments and depressed by our losses. Gradually, over the course of our individual development, we come to expect certain situations to produce certain types of feelings.

There are many chemical substances that have the power to alter this relationship between environment and feeling. Anxiety can be transformed into tranquility, exhilaration into sobriety, and torpor into vigor. When these substances are administered in a formal manner, they are called drugs, and the study of the effects of these drugs on mood and other behaviours defines the field of psychopharmacology.

Historically, the more common chemical substances that change behaviour have been plant products that were widely available and self-administered. Tea and opium were available in the Orient; tobacco and coffee in the Americas; and alcohol throughout the world. The substances were valued by each culture for the effects that they had on behaviour, but each culture also developed written or unwritten guidelines to regulate the use of the substances.

In addition to the commonly available plants, each geographic region has more obscure plants that may contain psychologically active substances. Information about the identifying features and effectiveness of these plants were passed on to family elders and to religious leaders. These individuals became valued for their knowledge of the effects of chemical substances, and became the informal practitioners of folk medicine. This gave way to the development of still more formal knowledge of these effects, and to the gradual development of formal medical practitioners.

Today, we have literally hundreds of different drugs that are known to change behaviour. Some of these have been borrowed directly from folk medicine and simply represent the modern processing and

reformulation of a drug application that may be centuries old. Others have been discovered by accident when a chemical reaction has gone awry or when a drug has been administered to treat one malady and it ends up being effective for some totally different problem. Although important contributions have been made from both of these sources, the vast majority of our modern drugs have been developed through systematic research on the relationships among drugs, behaviour, and the underlying chemistry of the brain.

CLASSIFICATION OF PSYCHOACTIVE DRUGS

Psychoactive drugs have two basic uses: (a) to alter mood and states of consciousness, and (b) to treat psychopathology.

Table 1 lists some examples of each type of drug.

Drugs that are used to alter moods and general states of consciousness can be divided into three broad categories based on the type of change they produce in the nervous system. Stimulant drugs produce an exaggeration of the conditions that are normally associated with alert wakefulness; in high dosages, these drugs produce overt seizure activity. Depressant drugs produce an exaggeration of the conditions that are normally associated with relaxation and sleep; in high dosages these drugs can produce unconsciousness. Hallucinogens produce a distortion of normal perception and thought processes; in high dosages these drugs can produce episodes of behaviour that can be characterized as psychotic. Although there are exceptions, a general rule is that these drugs produce their effects rather immediately by direct action on the neurons of the brain.

Drugs that are used to treat psychopathology can also be divided into three broad categories based on the type of symptoms that they can ameliorate. The antianxiety drugs are used to treat the day-to-day fears and anxieties of individuals who lead basically normal lives. The antidepressant drugs are used to treat feelings of negative affect that may range from mild melancholy to abject depression accompanied by suicidal tendencies. Finally, the antipyschotic drugs are used to treat severe forms of mental illness, most notably schizophrenia, in which patients lose contact with reality and engage in behaviours that fall considerably outside the realm of normalcy. Again, there are exceptions, but a general rule is that these drugs tend to act indirectly: Although they have immediate effects on the neurons of the brain, the therapeutic effects often require several weeks to appear, suggesting that the behavioural changes must await some long term, chronic adjustment of the neurons to the drug's actions (i.e., neuromodulation).

There are many drugs that are not listed in the general classification schema of Table 1. Such a table can never remain complete for very long because new drugs are continually being developed, new applications may be found for some drugs, old drugs are sometimes phased out of the marketplace, and new theory may change the boundaries of classification. Detailed and current information that would expand this table is compiled regularly and published in a variety of sources (e.g., Goodman & Gilman's The Pharmacological Bases of Therapeutics and the Physicians' Desk Reference). Paperback summaries of this information for prescription and nonprescription drugs are available in most bookstores and

libraries. We shall return to Table 1 later for a discussion of the mechanisms of actions for these drugs.

Click here to see Table 1.

SOME PRINCIPLES OF PHARMACOLOGY

In order for a drug to have an effect on behaviour, it must come into contact with the appropriate neurons in the brain. This can be accomplished in numerous ways, and the decision about the route of administration is based on a combination of factors including convenience, effects of the drug on local tissue, solubility of the drug, ionic characteristics of the drug, size of the drug molecule, and vulnerability of the drug to metabolism. The most common mode of administration is oral, with the drug being absorbed into the bloodstream through the walls of the stomach and intestines. Subcutaneous, transdermal, and intramuscular routes tend to produce slower and more sustained rates of delivery. Inhalation of drug vapors or injection of drugs directly into the bloodstream (intraarterial or intravenous) tend to produce very rapid onset of the drug effects. Minute quantities of drugs can be injected directly into the brain (intracranial) or into the spinal cord (intrathecal) to produce rapid effects that are restricted to the local area of injection.

The duration of drug action is determined primarily by the rate of metabolic inactivation of the drug. Most commonly, the drugs are metabolized into some inactive form by enzymes that are produced by the liver, the digestive tract, or by the nervous system tissue per se. These drug metabolites are removed from the body as waste products in the bowel, in the urine, through the skin, or by exhalation through the lungs. Drugs can sometimes be present in the body but have little or no effect because the drug molecules have been sequestered into a metabolically inactive pool. Examples of such pools include the bladder, fat deposits, or chemical bonding of drug molecules to larger protein molecules.

The relationship between the dosage of a drug and the response to that drug poses one of the thorniest problems in psychopharmacology. Common experience can provide a general description of the dose-response effect: For example, a sip of coffee will be subthreshold and will not help a student stay awake to study; a cupful will certainly help, and two might be better; five or six cups might lead to tremor and anxiety. These different responses to caffeine reflect the different concentrations of the drug in the blood. Technically, the lowest dose required to produce the desired effect (in 50% of the subjects) is termed the minimum effective dose (MED-50), and a dosage that is lethal to 50% of the subjects (the LD-50) is an index of the toxicity of the drug. The safety factor of a drug, the therapeutic index, is the ratio of LD-50/MED-50, which should be a large number (10 or more) to indicate that a lethal dose would be many times higher than the recommended dose.

Within the effective dose range, the responses may still be complicated. Typically, doubling the dosage does not double the effect, and many drugs show a bipolar dose-response curve. In the case of caffeine, for example, moderate doses can enhance typing skills but heavier doses begin to increase the number of errors. Furthermore, on tasks that are not well practiced, even low doses may impair performance; the dose-response relationship is determined as much by the details of the response as the details of the

drug's biochemistry.

The effects of a particular drug dosage also depend on the condition of the subject when the drug is administered. The law of initial values is an old concept that was first formulated to describe the effects of drugs on the cardiovascular system. Some drugs, for example, may be very effective in lowering blood pressure, but only if the blood pressure is abnormally high to begin with. This concept applies equally well in psychopharmacology, and is frequently referred to as the rate-dependency effect. Individuals who are already highly aroused may respond adversely to even small doses of a stimulant drug because it effectively increases the arousal to a level that interferes with performance. Similarly, many drugs that have antidepressant or antianxiety effects may produce relatively little change in the mood of individuals who are not suffering from depression or anxiety.

A particularly interesting drug effect is one that can occur when the dosage is zero. The placebo effect (placebo means "I will please") occurs when an inactive substance such as saline or a sugar capsule is represented as a drug, and leads to the relief of symptoms. This does not necessarily mean that either the initial symptoms or the relief of symptoms were imaginary. In the case of pain relief, for example, it is now clear that placebo effects are the result of the body's release of endogenous opiates in response to the belief that a drug was given. This type of behavioural effect is almost certainly a regular occurrence that increases or decreases the impact of real drug effects.

Given the intricate nature of the dose-response relationship, it should come as no surprise that subject variables play an important role. From childhood through senescence, there occur systematic changes in metabolism, body weight, and neurochemistry which can alter the effects of drugs. Hormonal differences between males and females, systematic differences in certain enzymes, and even cultural and climatic differences can further alter the effects of drugs. Finally, the individual's history of drug use may also produce long-term changes in metabolism of certain drugs that can either reduce their effectiveness (tolerance) or, less commonly, increase their effectiveness (sensitization). These contributing factors rarely appear on the labels of either prescription or nonprescription drugs, but should always be considered for patients who do not represent a typical category.

Drugs are not magic bullets-- even under the most carefully controlled conditions, a particular drug can either influence multiple neurotransmitter systems or multiple systems that use the same neurotransmitter. The pattern of this combination of effects can change with drug dosage. As a result, drugs frequently have undesirable side effects, but these complications may diminish with time or be controlled by adjusting the drug dosage. In many cases, the side effects of the drug may mimic the symptoms of some other disorder, for example, a drug that successfully treats depression might cause anxiety. The existence of side effects simply means that the effects of the drug on the brain are influencing pathways that are not specifically a part of the problem that was diagnosed.

The utility of any particular drug or elixir can be determined empirically. The successful treatment of previous patients can provide information about the most appropriate route of administration and dosage to use and the types of side effects to watch for. For example, if it is observed that alcohol can reduce

anxiety, the clinician might suggest that the anxious patient have a glass or two of wine with dinner. These types of observations and decisions have been useful in the development of folk medicines, but modern pharmacology relies more heavily on theory and mechanism. The development of a new and better drug treatment requires an understanding of both the disease process (i.e., the brain structures that are dysfunctional) and the way in which the drug alters this process (i.e., the neurochemical actions of the drug.) We turn now to a discussion of these mechanisms.

MECHANISMS OF DRUG ACTION IN THE BRAIN

One of the most elegant experiments in the history of pharmacology was performed in mid-1800's by a British physiologist named Claude Bernard. Explorers had brought back curare, a compound that native South Americans used as a poison on their blow gun darts to paralyse large mammals. Bernard was able to demonstrate that curare did not influence either the nerve fibers or the muscle fibers, but rather acted at the junction between these two structures.

Several decades later, Sir Charles Sherrington studied the special properties of the junction between one neuron and the next, and coined the term synapse to label this gap. He observed that the transmission of messages through the synapse differed in several ways from electric transmission through the nerve fiber: (a) messages passed in only one direction, (b) messages were changed as they travelled through the synapse, (c) messages were delayed at the synapse by 0.5 millisecond, and (d) some messages inhibited other messages. Knowledge of electricity was still in its infancy, but it was known that electric signals could not mimic these features of the synapse.

At the turn of the century, several researchers began to suspect that the transmission of messages across the synapse might involve chemicals. Many chemicals were known to influence the activity of the nervous system, and some of these (e.g., acetylcholine and noradrenaline) were present in the body. Although these chemicals could influence neuronal activity in laboratory preparations, there was no proof that they served as messengers under normal circumstances. The method of proof finally came to one of the researchers in a dream, and Otto Loewi went into his laboratory on Easter Sunday in 1921 to perform the critical experiment.

Loewi's experiment was elegant and simple. He dissected one frog's heart with a portion of the vagus nerve attached, a second heart without the vagus nerve, and placed them into separate containers of saline. Both hearts continued beating and, as expected from previous observations, electric stimulation of the vagus nerve caused the beating of the first heart to slow down. The clever part of the experiment was the pumping of the saline from the first beaker into the second. When this was done, the second heart also slowed down when the vagus nerve of the first heart was stimulated. There was no electric connection between the two hearts, and the only possible way that the message could be transmitted from one to the other was through the release of a chemical messenger into the surrounding fluid. Loewi dubbed the substance Vagusstoff (which turned out to be acetylcholine) and was later awarded the Nobel Prize for this first demonstration of the chemical transmission of neural messages.

Chemical messages could account for the special properties of the synapse observed by Sherrington. The release of a chemical messenger by one neuron onto the next would restrict the flow of information to one direction. Specific types of chemical messengers might be expected to inhibit rather than excite the next neuron. The chemical message would not be expected to maintain the specific temporal features of the volley of impulses that caused its release. Finally, the time required for the release and delivery of the chemical message could easily account for the 0.5-millisecond delay that Sherrington had observed. Despite all of these explanations, it still required a bold imagination in the 1920's to believe that tiny neurons could release several hundred chemical messages per second to conduct the complex functions of the nervous system.

Because of its accessibility and known functions, the peripheral autonomic nervous system became the natural choice as a test system for studying chemical transmission. Following Loewi's experiment, it soon became apparent that acetylcholine served as a chemical messenger in several locations. Not only was it released onto the heart muscle by the vagus nerve, but also onto the smooth muscles of all the organs and glands served by the parasympathetic system. Furthermore, acetylcholine was the messenger at the synapses in both the sympathetic and parasympathetic ganglia. It was also the messenger at the nerve-muscle junction for the striated muscles of voluntary movement (where the receptors can be blocked by curare, as in Bernard's experiment). But it became clear that acetylcholine was not the only neurotransmitter. Some other substance was being released onto the smooth muscles by the fibers of the sympathetic system, and that substance was determined to be noradrenaline, a substance very closely related to adrenaline, the hormone of the adrenal gland.

Now, the logic and the power of chemical transmission began to unfold. When different systems were anatomically separate as in the case of the separate locations of the sympathetic and parasympathetic ganglia, the same neurotransmitter could be used without confusion. But when two opposing systems projected to the same organ, for example the heart, then the release of different chemical messengers (e. g., acetylcholine to slow the heartbeat; noradrenaline to speed the heartbeat) could determine the different functions. But the autonomic nervous system was not going to yield all of the answers this simply:

A particular transmitter substance did not always produce the same effect. In the case of acetylcholine, there were two receptor types, muscarinic and nicotinic, which responded to different aspects of the molecule. Similarly, in the case of noradrenaline, there were also two receptor types, termed alpha and beta. The early researchers were eager to categorize these different receptor types into functional categories. The initial suspicions that acetylcholine was always inhibitory and noradrenaline was always excitatory had already been disconfirmed. The discovery of different receptor types for each compound held the possibility that these could be classified as excitatory or inhibitory. But it was not to be-- the specific receptor type is strictly for encoding the arrival of a message, and that message can be used as either a signal for excitation or inhibition.

While the details of chemical transmission were unfolding, other brain researchers had sought to relate anatomic structures of the brain to specific behavioural functions. Considerable progress was made in this effort, and research continues to sharpen the structure-function relationships. However, the

discovery of chemical transmission required that yet another layer of organization be added--neurons within a particular anatomic structure could have different neurotransmitters.

One of the clearest examples of this was a set of experiments done by S. P. Grossman in 1961. Previous research had demonstrated that lesions of the lateral hypothalamus produced a dramatic reduction in both eating and drinking, whereas electric stimulation elicited both eating and drinking. Grossman was able to separate these functions by applying different chemicals directly into the lateral hypothalamus through a chronically implanted cannula. Drugs that mimic acetylcholine elicited drinking only, whereas drugs that mimic noradrenaline elicited eating only. Drugs that block acetylcholine receptors reduced drinking in thirsty rats, whereas drugs that block noradrenaline receptors reduced eating in hungry rats. These results provided a finer grained analysis than the experiments that were based strictly on anatomy. Within the anatomic boundaries of the lateral hypothalamus are chemically coded functions for eating (noradrenergic) and drinking (cholinergic).

Given the knowledge that chemical coding at synapses is superimposed on anatomic subdivisions, we can now begin to understand how drugs can produce their specific effects on behaviour. The third column of Table 1 describes the action of the drug at the level of the individual neuron or synapse. As more cells are filled in on this table, we gain a better understanding of the relationship between behaviour and its underlying pharmacologic bases. Drugs can be classified, for examples, as mimickers of acetylcholine, blockers of specific receptor types, presynaptic blockers of activity, inhibitors of specific enzymes, and so forth. The list of neurotransmitters grew slowly at first (acetylcholine, noradrenaline, dopamine), but in the last decade or so, the list has exploded to more than 100 different chemicals, some of which are listed below:

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Types of Neurotransmitters

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Acetylcholine Peptides (several dozen)

Serotonin Enkephalins (opiate-like)

Adrenaline Leu-enkephalin

Dopamine Met-enkephalin

Noradrenaline Miscellaneous Types

Amino Acids GABA

Aspartate Taurine

Glycine Beta-alanine

Glutamate Nitric oxide

Others

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Drugs that influence behaviour must do so by influencing the brain, and there are several features of the brain that have contributed to a widespread misunderstanding of its basic character. Neurons, unlike most other cells, do not undergo cell division, so the brain contains virtually all of its cells at the time of birth. These cells are already committed to the general structure-function relationships that are seen in the adult brain, thus encouraging the view of the brain as a stable, organized set of neural circuits with individual experiences simply selecting different combinations of existing pathways; not unlike the structure of a computer (the hardware) that can be used for a host of different functions (the software).

This view of the brain as a static set of complex circuits is wrong. Although the general features and structure-function relationships are fixed, the details of neuronal actions are dynamic and constantly changing. When certain activity in the brain acts repeatedly to produce some behaviour, the circuits that are active can undergo physical changes (e.g., increased production of neurotransmitter molecules, expansion of the branching terminals of the axons, increased complexity of the receiving dendritic tree, increased number of receptors, etc.) which result in the enhanced efficiency of the system. The behaviour that is produced can produce changes in the environment, and changes in the environment (whether mediated by behaviour or not) can, in turn, produce changes in the brain.

A good way to conceptualize this is to view the brain, behaviour, and the environment as an interacting triangle, with each dimension influencing the other two (cf., Hamilton & Timmons, 1990). These interpenetrating effects require a more complex view of the results of various experimental manipulations. Although a particular drug may produce a very specific change in behaviour, we must not fall into the trap of viewing this as a singular effect. The neuronal systems that were directly influenced by the drug will also undergo a longer term change as a result of the drug's presence (and absence). The resulting behaviour will change the environment and that change will change other aspects of behaviour, and so forth. An appreciation of this dynamic interaction helps to provide a more complete understanding of the effects of drugs on behaviour.

The discipline of psychopharmacology in its modern form arose from the convergence of two separate areas of study: (a) the growing information about neurotransmission and the drugs that influenced it, and (b) B. F. Skinner's development of operant conditioning techniques for the study of behaviour. Skinner's methodology (e.g., Reynolds, 1975; see also Chapters 5.1 & 5.2) provided powerful methods for analyzing behavioural change, and numerous animal models began to emerge for the screening of

potentially useful drugs. The antipsychotic drugs rather specifically interfered with conditioned emotional responses, antianxiety drugs blocked the normal response to punishment, stimulant and depressant drugs changed general levels of activity, and so forth. The efficiency of these procedures greatly facilitated the accumulation of knowledge about the effects of drugs on behaviour, and became an indispensable link in the pathway of drugs from the chemist's bench to the pharmacist's shelf.

MECHANISMS OF DRUG ACTIONS ON BEHAVIOUR

Click here to see Table 1.

A. Drugs That Alter Moods and States of Consciousness

Central Nervous System Stimulants

Drugs can be classified as stimulants based on their ability to produce behavioural arousal, characteristic patterns of electroencephalographic (EEG) arousal, increases in motor activity, or some combination of these. These changes can be accomplished by several different mechanisms of action.

The so-called convulsant drugs such as strychnine, picrotoxin and pentylenetetrazol are representative of the different modes of action. Strychnine blocks the receptors for glycine, an inhibitory neurotransmitter. Picrotoxin reduces chloride permeability through its actions on the GABA receptor complex. (Gamma amino butyric acid, or GABA, is the most widespread neurotransmitter in the brain.) Pentylenetetrazol decreases the recovery time between action potentials by increasing potassium permeability of the axon. Drugs such as caffeine, theophylline and theobromine (present in coffee, tea, and chocolate) stimulate the activity of neurons by increasing the calcium permeability of membranes. Note that all of these drugs produce rather general effects that can influence neurons irrespective of the particular neurotransmitter system, and the state induced by these drugs is sometimes referred to as nonspecific arousal. In low to moderate dosages they can enhance learning and performance in a wide variety of situations, but with higher dosages, behaviour is impaired and dangerous seizures can be induced.

The amphetamines and cocaine may be the best known stimulant drugs, and both categories have rather specific effects on neurons that release dopamine or noradrenaline. Although the effects are not entirely specific, amphetamine stimulates these neurons by promoting the release of these neurotransmitters, while cocaine tends to block their reuptake. The restriction of the drug effects to a certain class of neurons is mirrored by a more specific change in behaviour. Some nonspecific arousal can be observed, but these two types of drugs have a profound effect in situations that involve specific behavioural responses that result in reward.

Central Nervous System Depressants

Drugs that are classified as central nervous system depressants appear to act on two major neurotransmitter systems. One of the neurotransmitters of sleep is serotonin, and certain drugs that

enhance the activity of serotonin can induce drowsiness and sleep. The other important neurotransmitter is GABA, and the more common sedative and hypnotic drugs (e.g., the benzodiazepines, barbiturates, and alcohol) tend to produce their effects by acting on the GABA receptor complex. Acting on a special receptor site, they facilitate the action of GABA and inhibit neuronal activity by increasing the permeability of the neuronal membranes to chloride ions.

The narcotic drugs deserve special mention as CNS depressants. Extracts of the opium poppy have been used for thousands of years for both medicinal (pain relief) and recreational (general sense of well being) effects. Opium (a mixture of morphine and codeine) is naturally occurring, whereas heroin is a synthetic drug. The powerful effects of these drugs could not be explained by their actions on any of the known neurotransmitters. Finally, in the 1970's, it was determined that some neurons had specific receptors for these compounds, and that the body produced a variety of different substances (some chemical neurotransmitters and some hormones) that acted like the narcotic drugs. These endogenous morphine-like substances, termed endorphins, are released in response to various types of pain or stress.

Hallucinogens

Although drugs that stimulate or depress the general activity of the brain lead to changes in the interaction with the environment, these changes tend to be more quantitative than qualitative. Hallucinogens, on the other hand, produce fundamental changes in the sensorium. Visual and auditory distortions and imagery may be experienced. Tactile sensations may occur without stimulus. In some cases there may occur a conflation of experiences, called synesthesia, in which visual experiences may be "heard" or tactile experiences "seen" in ways that almost never occur in the absence of the drug. The drugs that produce these changes are derived from a variety of different plant sources as well as synthetic sources and tend to produce changes in many different neurotransmitter systems. The mechanism of action that causes the hallucinations remains clouded, but there is a growing consensus that these drugs act on serotonin receptors.

Some Observations on Abuse and Addiction

If a drug is administered repeatedly, there is frequently a reduction in the effectiveness of the drug, called tolerance. This can occur through several different mechanisms: (a) liver enzymes may be induced to speed up drug degradation; (b) presynaptic neurons may increase or decrease the production of neurotransmitters; (c) postsynaptic neurons may increase or decrease the number of receptors; and (d) opposing systems may increase or decrease their activity. Typically, more than one of these countermeasures is launched, and the brain's activity gradually becomes more normalized despite the presence of the drug.

Tolerance sets the stage for another phenomenon. If the drug administration is suddenly stopped, the mechanisms of tolerance are unmasked and withdrawal symptoms occur. As a result of the mechanisms of tolerance, the brain functions more normally in the presence of a drug than in its absence.

The types of tolerance described above are referred to as pharmacological tolerance. These mechanisms cannot always account for the observed decline in response to the drug. For example, amphetamine reduces the amount of milk that rats will drink during a daily session, but by the tenth day, drinking has returned to normal levels. However, if the drug is administered alone for 10 days, and milk is offered on the 11th day, the drug still suppresses drinking. The return to normal drinking requires learning to perform the behaviour in the presence of the drug. This type of effect is known as behavioural tolerance (Carlton & Wolgin, 1971).

The facts that many drugs have direct rewarding effects and that tolerance can develop to these rewarding effects can lead to motivation for self-administration of drugs. Drugs that have the capacity to produce such motivation typically share three characteristics: (a) they act on the central nervous system, (b) they act rapidly, and (c) the cessation of use produces withdrawal symptoms. These characteristics can produce an acquired motivational state (i.e., a desire or motivation for the effects of the drug) which can lead to addiction or abuse of the drug. The narcotic drugs are among the most potent in this regard.

Just as some individuals may be more sensitive to the effects of a drug because of differences in metabolism, specific neurotransmitter activity, or other subject variables, so might some individuals be more susceptible to acquiring the motivational states that we call addiction or substance abuse. There is growing evidence that this susceptibility may have a genetic basis. In the case of alcohol abuse, for example, there is a clear tendency for sons of alcoholics to be more likely to become alcoholics, and preliminary evidence points to a genetic defect that may alter the response to reward (e.g., Blum, 1991; see also Chapters 2.1 & 10.5). This and related evidence may soon provide a physiologic basis for the somewhat ill-chosen term, addictive personality.

B. Drugs Used to Treat Disorders of Behaviour

Click here to see Table 1.

Antipsychotics

The discovery of the drugs that are used to treat psychoses (primarily schizophrenia) followed a strange and fascinating pathway. A French surgeon, Henri Laborit, was convinced in the 1940's that many of the deaths associated with surgery could be attributed to the patients' own fears about the dangers of surgery. Attempts to reduce this distress with sedatives or by blocking the autonomic nervous system were only marginally effective. Laborit concluded that what was needed was a drug that could dissolve the fear response itself-- in his words, a Pavlovian deconditioner. His search led to one of the newly developed antihistamine compounds (promethazine), and a variant of this compound, chlorpromazine, proved to be dramatically effective. Patients who received this drug presurgically were calm, minimally sedated, and the incidence of deaths from surgical shock was greatly reduced.

Soon, of course, the use of chlorpromazine spread to the psychiatric clinic and was found to produce an equally dramatic reversal of the symptoms of schizophrenia. Chlorpromazine and related phenothiazine

drugs were responsible for the release of hundreds of thousands of patients from institutions where they otherwise would have spent the remainder of their lives in heavy sedation, in straightjackets, or other restraints. The patients were not cured, but for many, they were able for the first time in years to engage in relatively normal day-to-day interactions.

Laborit's characterization of chlorpromazine as a Pavlovian deconditioner was upheld. In proper doses, the phenothiazines can specifically reduce signaled avoidance responding in animals while not influencing the direct response to an aversive stimulus. More recently, an even more specific animal (and human) model of this disorder has been developed by Jeffrey Gray and his colleagues at the University of London (see Baruch, Hemsley & Gray, 1988). They view much of the anxiety associated with schizophrenia as being the result of a discordance between current perceptions and perceived regularities of past events. For example, normal individuals who have heard 30 presentations of a bell do not readily acquire a conditioned response if this bell is now paired with electric shock-- a phenomenon known as latent inhibition. Patients suffering from schizophrenia are impaired in latent inhibition (i.e., do not learn that the bell was "safe"), and this deficit is normalized by chlorpromazine.

These antipsychotic drugs produce a variety of effects on neurons, but almost certainly produce their beneficial effects by blocking the D2 receptor for dopamine. When all of the drugs in common clinical use are rank ordered according to their potency, the rank ordering is identical to that achieved when they are rank ordered according to their ability to block the D2 receptor. A similar order is obtained when they are ranked according to their specific ability to inhibit avoidance responding, and given time, there will almost certainly be a similar concordance when rank ordered in terms of their effects on latent inhibition.

These close relationships between clinically useful drugs, animal models, affinity to specific receptors and theoretical models of neurotransmitters and behaviour have brought us to a point where it is not unrealistic to suppose that schizophrenia can be understood in the foreseeable future, perhaps even prevented or cured.

Antianxiety Drugs

The success of chlorpromazine in dissolving the acute fears that surround surgery as well as the pervasive fears that torment the psychotic mind led to the search for milder drugs that could allay more commonplace anxieties. The barbiturate drugs (and alcohol) had been used with some success, but dosages that reduced anxiety also produced troublesome side effects of sedation. This situation led to the marketing of meprobamate, which was claimed to ease anxiety without sedation. This drug became very popular, even though it was in fact just a mild barbiturate that had as many sedative effects as the other drugs in this class.

Although meprobamate did not live up to its initial promise, the claims of specificity did promote the search for other drugs that could have these effects. By the early 1960's, two such drugs (chlordiazepoxide and diazepam) had been discovered. Marketed under the trade names of Librium and

Valium, these drugs quickly became the most widely prescribed drugs of their time.

Chlordiazepoxide and related benzodiazepine compounds were initially termed minor tranquilizers (as contrasted with the antipsychotics that were known as major tranquilizers), but this terminology fell into disfavor and they are now known simply as antianxiety compounds. Nearly all of the compounds in this class act by facilitating the activity of the neurotransmitter GABA. The so-called GABA receptor complex is a complicated structure that has (a) a GABA site, (b) a sedative/convulsant site, and (c) a benzodiazepine site. There is now growing evidence that the brain manufactures its own antianxiety compounds as neurotransmitters that are released during periods of stress.

Antidepressants

Antidepressants are drugs that help to reverse mood states which are characterized by sadness, lack of self esteem, and general depression. A variety of animal models of this disorder has linked depression to the monoamines, especially noradrenaline and serotonin.

The first drugs to be used in the treatment of depression were discovered by accident. Tuberculosis patients who were being treated with a new drug called iproniazid seemed to be enjoying a remarkable recovery, but it was soon learned that while their tuberculosis remained unaffected, their understandable mood of depression was being elevated by the drug. It was later learned that iproniazid and related drugs inhibit the activity of an enzyme known as monoamine oxidase (MAO), and tend to gradually elevate the level of activity of neurons that utilize dopamine or noradrenaline as neurotransmitters.

The search for better and safer drugs to treat depression led to the discovery of a class of compounds called the tricyclic antidepressants, so named because their basic chemical structure includes three carbon rings. Most of these compounds appear to act by blocking the reuptake of dopamine and noradrenaline, but some of them also block the reuptake of serotonin, some block serotonin alone, and some have no known effect on any of these systems.

Some patients who suffer from depression also have recurrent episodes of manic behaviour. This disorder, known as bipolar disorder, is treated most successfully by the administration of lithium salts. Lithium tends to stabilize the neurons, preventing the development of mania that is usually followed by a period of deep depression. The neuronal mechanism remains somewhat mysterious, although recent evidence suggests that lithium blocks the synthesis of a second messenger, a neuronal compound that promotes long-term changes in the general capacity for synaptic activity.

FUTURE DIRECTIONS

The future of psychopharmacology contains many challenges. Certainly one of the major challenges is to understand the biological bases of substance abuse in sufficient detail to allow the prevention and treatment of these devastating disorders. The foundations for this are already in place: The neurotransmitters and anatomic circuitry of the reward system are known in some detail; the psychology

of reward and motivational systems has unravelled many of the behavioural contributions to substance abuse; and genetic studies have begun to demonstrate the possibility of predicting and understanding individual differences in the vulnerability of these systems.

A second set of challenges involves the development of more specific drugs ("magic bullets") which can restore the victims of depression, schizophrenia, anxiety, and other disorders to normalcy. Again, the development of these drugs will require a detailed understanding of the neurotransmitters, specific receptor types, and sophisticated understanding of the behavioural contributions to the disorders.

A third, related set of challenges will be to provide drugs that treat and otherwise modify behaviours that are of day-to-day concern for many people. Drugs that can facilitate memory, counteract the effects of aging on cognitive abilities, normalize food intake, and so forth. Some might claim that the availability of more drugs will only serve to exacerbate the problems that we already face with drug abuse. However, drug use and abuse are as old as humankind, and we can only benefit from a better understanding of the effects of drugs on the brain's control of behaviour.

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VOCABULARY WORDS

Acetylcholine

Acquired motivational state

Addictive personality

Adrenaline

Alcohol

Alpha receptors

Amphetamine

Antianxiety drugs

Antidepressants

Antipsychotic drugs

Barbiturates

Behavioural tolerance

Benzodiazepine

Benzodiazepines

Beta receptors

Bipolar disorder

Blockers

Caffeine

Chemical transmission

Chlordiazepoxide

Chlorpromazine

Cocaine

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Iproniazid

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Valium

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Drug Index

Categorical List
Alphabetical List A B C D E F G H I J K L M N O P Q R S T U V W X Y Z

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amantadine hydrochloride
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amitriptyline hydrochloride
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Anxanil
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mephobarbital
Mephoral

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protriptyline hydrochloride
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selegiline hydrochloride; L-deprenyl hydrochloride
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Sereen
Serentil
Sertan
sertraline hydrochloride
Sinequan
SK-Amitriptyline
SK-Bamate
SK-Lygen
SK-Pramine
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Stelazine
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thioridazine hydrochloride
thiothixene; thiothixene hydrochloride
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Thorazine
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Tranmep
Tranxene-SD
tranylcypromine sulfate
trazodone hydrochloride
Tremin
Trialodine
triazolam
Tridione
trifluoperazine hydrochloride
Trihexane
Trihexidyl
Trihexy-2; Trihexy-5
trihexyphenidyl hydrochloride
Trilafon
trimethadione
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Valrelease
Vamate
venlafaxine hydrochloride
Versed
Vistacon
Vistaject
Vistaquel
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Vistazine
Vivactil

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Xanax

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Zarontin
Zoloft
zolpidem tartrate

A

Generic name: **acetophenazine maleate**
Trade name(s): Tindal
Class: piperazine phenothiazine
Type: Antipsychotic
Indications: Psychotic disorders

Generic name: **alprazolam**
Trade name(s): Xanax
Class: triazolo benzodiazepine
Type: Antianxiety
Indications: Anxiety and tension; Panic disorder

Generic name: **amantadine hydrochloride**
Trade name(s): Symmetrel
Class: cyclic primary amine
Type: Antiparkinson
Indications: Drug-induced extrapyramidal reactions; Parkinsonian syndrome

Generic name: **amitriptyline hydrochloride**
Trade name(s): Amitriptylene; Elavil; Emitrip; Endep; Enovil; SK-Amitriptyline
Class: tertiary tricyclic
Type: Antidepressant
Indications: Depression; anorexia or bulimia associated with depression; adjunctive treatment of neurogenic pain

Generic name: **amobarbital; amobarbital sodium**
Trade name(s): Amytal
Class: barbiturate
Type: Sedative-Hypnotic; Anticonvulsant
Indications: Sedation; Insomnia; Adjunct in psychotherapy; Anticonvulsant

Generic name: **amoxapine**
Trade name(s): Asendin
Class: tricyclic dibenzoxazepine,
Type: Antidepressant
Indications: Depression

Generic name: **aprobarbital**
Trade name(s): Alurate
Class: barbiturate

Type: Sedative-Hypnotic
Indications: Sedation; Insomnia

B

Generic name: **bupropion hydrochloride**
Trade name(s): Wellbutrin
Class: monocyclic aminoketone
Type: Antidepressant
Indications: Depression

Generic name: **buspirone hydrochloride**
Trade name(s): BuSpar
Class: azaspirodecanedione derivative
Type: Antianxiety
Indications: Anxiety

Generic name: **butabarbital**
Trade name(s): Barbased; Butalan; Buticaps; Butisol; Butatran; Sarisol No. 2
Class: barbiturate
Type: Sedative-Hypnotic
Indications: Sedation; Insomnia

C

Generic name: **carbamazepine**
Trade name(s): Epitol; Mazepine; Tegretol
Class: tricyclic iminostilbene antidepressant
Type: Anticonvulsant; Analgesic
Indications: Generalized tonic-clonic, complex-partial, mixed seizure patterns, rapid seizure control; Trigeminal neuralgia; bipolar affective disorder,intermittent explosive disorder; alcohol withdrawal; benzodiazepine withdrawal; diabetes insipidis

Generic name: **chloral hydrate**
Trade name(s): Aquachloral; Noctec; Novochlorhydrate
Class: general central nervous system depressant
Type: Sedative-Hypnotic
Indications: Sedation; Insomnia; Hypnosis

Generic name: **chlordiazepoxide**
Trade name(s): Libritabs
Class: 2-keto benzodiazepine

Type: Antianxiety; Anticonvulsant; Sedative-hypnotic
Indications: Anxiety and tension; Alcohol withdrawal

Generic name: **chlordiazepoxide hydrochloride**
Trade name(s): Librium; Lipoxide; SK-Lygen; Murcil; Reposans-10; Sereen
Class: 2-keto benzodiazepine
Type: Antianxiety; Anticonvulsant; Sedative-hypnotic
Indications: Anxiety and tension; Alcohol withdrawal

Generic name: **chlorpromazine hydrochloride**
Trade name(s): Chlorzine; Ormazine; Promapar; Promaz; Sonazine; Thorazine; Thor-Prom
Class: aliphatic phenothiazine
Type: Antipsychotic
Indications: Psychosis; Acute agitation; Nausea and vomiting; Mild alcohol withdrawal

Generic name: **chlorprothixene; chlorprothixene hydrochloride**
Trade name(s): Taractan
Class: thioxanthene
Type: Antipsychotic
Indications: Psychotic disorders; Agitation of severe neurosis, depression, schizophrenia

Generic name: **clomipramine hydrochloride**
Trade name(s): Anafranil
Class: tertiary tricyclic
Type: Antiobsessional agent; antidepressant
Indications: Obsessive-compulsive disorder

Generic name: **clonazepam**
Trade name(s): Klonopin; Rivotril
Class: 3-hydroxy benzodiazepine
Type: Anticonvulsive
Indications: Absence and atypical absence seizures, akinetic and myoclonic seizures; Nocturnal myoclonus; bipolar disorder

Generic name: **clonidine hydrochloride**
Trade name(s): Catapres; Catapres-TTS
Class: imidazoline
Type: Antihypertensive
Indications: Hypertension; adjunctive therapy in nicotine withdrawal; adjunctive therapy in opiate withdrawal

Generic name: **clorazepate dipotassium**

Trade name(s): Tranxene-SD
Class: 2-keto benzodiazepine
Type: Antianxiety; Anticonvulsant; Sedative-hypnotic
Indications: Anxiety; Acute alcohol withdrawal; Adjunct in epilepsy

Generic name: **clozapine**
Trade name(s): Clozaril
Class: tricyclic dibenzodiazepine derivative
Type: Antipsychotic
Indications: Drug-resistent Schizophrenia

D

Generic name: **desipramine hydrochloride**
Trade name(s): Norpramin; Pertofrane
Class: secondary tricyclic dibenzazepine
Type: Antidepressant; Antianxiety
Indications: Depression

Generic name: **dextroamphetamine sulfate**
Trade name(s): Dexampex; Dexedrine; Ferndex; Oxydess II; Robese; Spancap #1
Class: amphetamine
Type: Stimulant
Indications: Narcolepsy; Attention deficit disorders with hyperactivity; short-term adjunct in exogenous obesity

Generic name: **diazepam**
Trade name(s): Valium; Valrelease
Class: 2-keto benzodiazepine
Type: Antianxiety; Skeletal muscle relaxant; Amnesic agent; Anticonvulsant; Sedative-hypnotic
Indications: Anxiety and tension; Acute alcohol withdrawal; Adjunct to skeletal muscle spasm; Adjunct to convulsant disorders; Status epilepticus

Generic name: **diphenhydramine**
Trade name(s): non prescription
Class: ethanolamine antihistamine
Type: Sedative-hypnotic
Indications: Insomnia

Generic name: **divalproex sodium**
Trade name(s): Depakote
Class: carboxylic acid derivative

Type: Anticonvulsant
Indications: Simple and complex absence seizures and mixed seizure types

Generic name: **doxepin hydrochloride**
Trade name(s): Adapin; Sinequan
Class: tertiary tricyclic
Type: Antidepressant
Indications: Depression

E

Generic name: **estazolam**
Trade name(s): ProSom
Class: triazolo benzodiazepine
Type: Hypnotic
Indications: Short-term management of insomnia characterized by difficulty in falling asleep, frequent nocturanl awakenings, or early-morning awakenings

Generic name: **ethchlorvynol**
Trade name(s): Placidyl
Class: chlorinated tertiary acetylenic carbinol
Type: Sedative-Hypnotic
Indications: Sedation; Insomnia

Generic name: **ethosuximide**
Trade name(s): Zarontin
Class: succinimide derivative
Type: Anticonvulsant
Indications: Absence seizures

Generic name: **ethotoin**
Trade name(s): Peganone
Class: hydantoin derivative
Type: Anticonvulsant
Indications: Generalized tonic-clonic or complex-partial seizures

F

Generic name: **fluoxetine**
Trade name(s): Prozac
Class: bicyclic serotonin uptake inhibitor
Type: Antidepressant

Indications: Depression; Obsessive-compulsive disorder; panic disorder

Generic name: **fluphenazine decanoate**
Trade name(s): Prolixin Decanoate
Class: piperazine phenothiazine
Type: Antipsychotic
Indications: Psychotic disorders

Generic name: **fluphenazine enanthate**
Trade name(s): Prolixin Enanthate
Class: piperazine phenothiazine
Type: Antipsychotic
Indications: Psychotic disorders

Generic name: **fluphenazine hydrochloride**
Trade name(s): Permitil hydrochloride; Prolixen hydrochloride
Class: piperazine phenothiazine
Type: Antipsychotic
Indications: Psychotic disorders

Generic name: **flurazepam hydrochloride**
Trade name(s): Dalmane; Durapam
Class: 2-keto benzodiazepine
Type: Sedative-Hypnotic
Indications: Insomnia

Generic name: **fluvoxamine**
Trade name(s): Luvox
Class: serotonin reuptake inhibitor
Type: Antidepressant; Antiobsessional
Indications: ???

G

Generic name: **gabapentin**
Trade name(s): Neurontin
Class: 1-aminomethyl cyclohexonacetic acid
Type: Anticonvulsant
Indications: Adjunctive treatment of partial seizures with and without secondary generalization

Generic name: **glutethimide**
Trade name(s): Doriden; Doriglute

Class: piperidinedione
Type: Sedative-hypnotic
Indications: Insomnia

H

Generic name: **halazepam**
Trade name(s): Paxipam
Class: benzodiazepine
Type: Antianxiety
Indications: Relief of anxiety and tension

Generic name: **haloperidol decanoate**
Trade name(s): Haldol decanoate
Class: butyrophenone
Type: Antipsychotic
Indications: Psychotic disorders; Control of tics, vocal utterances in Gilles de la Tourette's syndrome

Generic name: **haloperidol; haloperidol lactate**
Trade name(s): Haldol
Class: butyrophenone
Type: Antipsychotic
Indications: Psychotic disorders; Control of tics, vocal utterances in Gilles de la Tourette's syndrome

Generic name: **hydroxyzine hydrochloride**
Trade name(s): Anxanil; Atarax; Atozine; Durrax; E-Vista; Hydroxacen; Hyzine; Orgatrex; Quiess; Vistacon; Vistaject; Vistaquel; Vistazine
Class: piperazine dihydrochloride antihistamine
Type: Antianxiety; Sedative
Indications: Anxiety and tension; Anxiety, tension, hyperkinesia; Pre- and Post-operative sedation

Generic name: **hydroxyzine pamoate**
Trade name(s): Hy-Pam; Vamate; Vistaril
Class: piperazine dihydrochloride antihistamine
Type: Antianxiety; Sedative
Indications: Anxiety and tension; Anxiety, tension, hyperkinesia; Pre- and Post-operative sedation

I

Generic name: **imipramine hydrochloride**
Trade name(s): Janimine; SK-Pramine; Tofranil; Typramine
Class: tertiary dibenzazepine tricyclic

Type: Antidepressant
Indications: Depression; Childhood enuresis; neurogenic pain; panic disorder; generalized anxiety disorder

Generic name: **imipramine pamoate**
Trade name(s): Tofranil-PM
Class: tertiary dibenzazepine tricyclic
Type: Antidepressant
Indications: Depression; Childhood enuresis; neurogenic pain; panic disorder; generalized anxiety disorder

Generic name: **isocarboxazid**
Trade name(s): Marplan
Class: hydrazine monoamine-oxidase inhibitor
Type: Antidepressant
Indications: discontinued in 1994

J

K

L

Generic name: **lithium carbonate**
Trade name(s): Eskalith; Eskalith CR; Lithane; Lithobid; Lithonate; Lithotabs
Class: alkali metal
Type: Antimanic; Antipsychotic
Indications: Prevention or control of mania; Prevention of depression in patients with bipolar disorder; Apparent mixed bipolar disorder in children; major depression; schizoaffective disorder; schizophrenic disorder; alcohol dependence

Generic name: **lithium citrate**
Trade name(s): Cibalith-S
Class: alkali metal
Type: Antimanic; Antipsychotic
Indications: Prevention or control of mania; Prevention of depression in patients with bipolar disorder; Apparent mixed bipolar disorder in children; major depression; schizoaffective disorder; schizophrenic disorder; alcohol dependence

Generic name: **lorazepam**
Trade name(s): Alzapam; Ativan; Loraz
Class: 3-hydroxy benzodiazepine

Type: Antianxiety; Sedative-hypnotic
Indications: Anxiety,tension,agitation,irritability,especially in anxiety neurosis or organic (especially GI or CV) disorders; Insomnia; Staus epilepticus; preoperative sedative

Generic name: **loxapine hydrochloride**
Trade name(s): Loxitane C; Loxitane IM
Class: dibenzoxazepine
Type: Antipsychotic
Indications: Psychotic disorders

Generic name: **loxapine succinate**
Trade name(s): Loxitane
Class: dibenzoxazepine
Type: Antipsychotic
Indications: Psychotic disorders

M

Generic name: **magnesium sulfate**
Trade name(s): Magnesium sulfate
Class: mineral; electrolyte
Type: Anticonvulsant
Indications: Hypomagnesemic seizures; Prevention or control of seizures in eclampsia

Generic name: **maprotoline hydrochloride**
Trade name(s): Ludiomil
Class: tetracyclic
Type: Antidepressant
Indications: Depression

Generic name: **mephenytoin**
Trade name(s): Mesantoin
Class: hydantoin derivative
Type: Anticonvulsant
Indications: Generalized tonic-clonic or complex-partial seizures

Generic name: **mephobarbital**
Trade name(s): Mebaral; Mentaban; Mephoral
Class: barbiturate
Type: Anticonvulsant; CNS depressant
Indications: Generalized tonic-clonic or absence seizures

Generic name: **meprobamate**
Trade name(s): Equinil; Meprospan; Miltown; Neuramate; Neurate; Sedabamate; SK-Bamate; Tranmep
Class: carbamate
Type: Antianxiety
Indications: Anxiety and tension

Generic name: **mesoridazine besylate**
Trade name(s): Serentil
Class: piperidine phenothiazine
Type: Antipsychotic
Indications: Psychoneurotic manifestations (anxiety); Schizophrenia; Alcoholism; Behavioral problems associated with chronic brain syndrome

Generic name: **methamphetamine hydrochloride**
Trade name(s): Desoxyn; Methampex
Class: amphetamine
Type: Stimulant
Indications: Attention deficit disorder with hyperactivity; Short-term adjunct in exogenous obesity

Generic name: **methotrimeprazine hydrochloride**
Trade name(s): Levoprome
Class: propylamino phenothiazine
Type: Sedative; Analgesic
Indications: Sedation, analgesia

Generic name: **methsuximide**
Trade name(s): Celontin Kapseals
Class: succinimide
Type: Anticonvulsant
Indications: Refractory absence seizures

Generic name: **methylphenidate hydrochloride**
Trade name(s): Methidate; Ritalin; Ritalin SR
Class: piperidine central nervous system stimulant
Type: Stimulant
Indications: Attention deficit disorder with hyperactivity; Narcolepsy

Generic name: **midazolam hydrochloride**
Trade name(s): Versed
Class: benzodiazepine
Type: Sedative
Indications: Preoperative sedation

Generic name: **molindone hydrochloride**
Trade name(s): Moban
Class: dihydroindolone
Type: Antipsychotic
Indications: Psychotic disorders

N

Generic name: **nortriptyline hydrochloride**
Trade name(s): Aventyl; Pamelor
Class: secondary tricyclic
Type: Antidepressant
Indications: Depression; panic disorder

O

Generic name: **oxazepam**
Trade name(s): Serax
Class: 3-hydroxy benzodiazepine
Type: Antianxiety; Sedative-hypnotic
Indications: Alcohol withdrawal; Severe anxiety; Tension, mild to moderate anxiety

P

Generic name: **paramethadione**
Trade name(s): Paradione
Class: oxazolidinedione derivative
Type: Anticonvulsant
Indications: Refractory absence seizures

Generic name: **paroxetine hydrochloride**
Trade name(s): Paxil
Class: serotonin reuptake inhibitor
Type: Antidepressant
Indications: Depression

Generic name: **pemoline**
Trade name(s): Cylert
Class: oxazolidinedione derivative
Type: Stimulant; Analeptic
Indications: Attention deficit disorder; Narcolepsy

Generic name: **pentobarbital sodium**
Trade name(s): Nembutal
Class: barbiturate
Type: Anticonvulsant; Sedative-Hypnotic
Indications: Sedation; Insomnia; Anticonvulsant

Generic name: **perphenazine**
Trade name(s): Trilafon
Class: piperazine phenothiazine
Type: Antipsychotic
Indications: Psychosis; Mental disturbances, acute alcoholism, nausea, vomiting,hiccups

Generic name: **phenacemide**
Trade name(s): Phenurone
Class: substituted acetylurea derivative, open-chain hydantoin
Type: Anticonvulsant
Indications: Refractory, complex-partial, generalized tonic-clonic, absence, and atypical absence seizures

Generic name: **phenelzine sulfate**
Trade name(s): Nardil
Class: hydrazine monoamine-oxidase inhibitor
Type: Antidepressant
Indications: Severe depression; panic disorder

Generic name: **phenobarbital**
Trade name(s): Barbita; Solfoton
Class: barbiturate
Type: Anticonvulsant; Sedative-Hypnotic
Indications: All forms of epilepsy except absence seizures, febrile seizures in children; Status epilepticus; Sedation; Insomnia

Generic name: **phenobarbital sodium**
Trade name(s): Luminal
Class: barbiturate
Type: Anticonvulsant; Sedative-Hypnotic
Indications: All forms of epilepsy except absence seizures, febrile seizures in children; Status epilepticus; Sedation; Insomnia

Generic name: **phensuximide**
Trade name(s): Milontin
Class: succinimide derivative
Type: Anticonvulsant

Indications: Absence seizures

Generic name: **phenytoin; phenytoin sodium**
Trade name(s): Dilantin; Di-Phen; Diphenylan
Class: hydantoin
Type: Anticonvulsant
Indications: Generalized tonic-clonic seizures, status epilepticus,nonepileptic seizures; Neuritic pain

Generic name: **pimozide**
Trade name(s): Orap
Class: diphenylbutylpiperdine
Type: Antipsychotic
Indications: Suppression of severe motor and phonic tics in patients with Gilles de la Tourette's syndrome

Generic name: **prazepam**
Trade name(s): Centrax
Class: 2-keto benzodiazepine
Type: Antianxiety
Indications: Anxiety

Generic name: **primidone**
Trade name(s): Myidone; Mysoline; Sertan
Class: barbiturate analogue
Type: Anticonvulsant
Indications: Generalized tonic-clonic seizures, complex-partial (psychomotor) seizures

Generic name: **prochlorperazine maleate**
Trade name(s): Chlorazine; Compazine; Compazine Spansule
Class: piperazine phenothiazine
Type: Antipsychotic; Antianxiety
Indications: Psychosis

Generic name: **prochlorperazine; prochlorperazine edisylate**
Trade name(s): Compazine
Class: piperazine phenothiazine
Type: Antipsychotic; Antianxiety
Indications: Psychosis

Generic name: **promazine hydrochloride**
Trade name(s): Prozine; Sparine
Class: aliphatic phenothiazine

Type: Antipsychotic
Indications: Psychosis

Generic name: **protriptyline hydrochloride**
Trade name(s): Triptil; Vivactil
Class: secondary tricyclic
Type: Antidepressant
Indications: Depression

Q

Generic name: **quazepam**
Trade name(s): Doral
Class: benzodiazepine
Type: Hypnotic
Indications: Insomnia

R

Generic name: **risperidone**
Trade name(s): Risperdal
Class: benzisoxazole derivative
Type: Antipsychotic
Indications: Psychosis

S

Generic name: **secobarbital sodium**
Trade name(s): Seconal; Tuinal
Class: barbiturate
Type: Sedative-Hypnotic; Anticonvulsant
Indications: Preoperative sedation; Insomnia; Acute psychotic agittion; Status epilepticus

Generic name: **selegiline hydrochloride; l-deprenyl hydrochloride**
Trade name(s): Eldepryl
Class: monoamine-oxidase inhibitor
Type: Antiparkinson
Indications: Adjunctive therapy for Parkinson's disease

Generic name: **sertraline hydrochloride**
Trade name(s): Zoloft
Class: serotonin reuptake inhibitor

Type: Antidepressant
Indications: Depression; Obsessive-compulsive disorder

T

Generic name: **temazepam**
Trade name(s): Razepam; Restoril; Temaz
Class: 3-hydroxy benzodiazepine
Type: Sedative-Hypnotic
Indications: Insomnia

Generic name: **thioridazine**
Trade name(s): Mellaril-S
Class: piperidine phenothiazine
Type: Antipsychotic
Indications: Psychosis; Dysthymic disorder (neurotic depression), alcohol withdrawal,dementia in geriatric patients, behavior problems in children

Generic name: **thioridazine hydrochloride**
Trade name(s): Mellaril; Millazine
Class: piperidine phenothiazine
Type: Antipsychotic
Indications: Psychosis; Dysthymic disorder (neurotic depression), alcohol withdrawal,dementia in geriatric patients, behavior problems in children

Generic name: **thiothixene; thiothixene hydrochloride**
Trade name(s): Navane
Class: thioxanthene
Type: Antipsychotic
Indications: Acute agitation; Psychosis

Generic name: **tranylcypromine sulfate**
Trade name(s): Parnate
Class: monoamine-oxidase inhibitor
Type: Antidepressant
Indications: Severe depression; panic disorder

Generic name: **trazodone hydrochloride**
Trade name(s): Desyrel; Trialodine
Class: triazolopyridine
Type: Antidepressant
Indications: Depression

Generic name: **triazolam**
Trade name(s): Halcion
Class: triazolam benzodiazepine
Type: Sedative-Hypnotic
Indications: Insomnia

Generic name: **trifluoperazine hydrochloride**
Trade name(s): Stelazine; Suprazine
Class: piperazine phenothiazine
Type: Antipsychotic
Indications: Anxiety states; Schizophrenia and other psychotic disorders

Generic name: **trihexyphenidyl hydrochloride**
Trade name(s): Aphen; Artane; Artane Sequels; Tremin; Trihexane; Trihexidyl; Trihexy-2; Trihexy-5
Class: anticholinergic
Type: Antiparkinson
Indications: Drug-induced parkinsonism

Generic name: **trimethadione**
Trade name(s): Tridione
Class: oxazolidinedione derivative
Type: Anticonvulsant
Indications: Refractory absence seizures

Generic name: **trimipramine maleate**
Trade name(s): Surmontil
Class: tertiary tricyclic
Type: Antidepressant; Antianxiety
Indications: Depression

U

V

Generic name: **valproic acid**
Trade name(s): Depakene
Class: carboxylic acid derivative
Type: Anticonvulsant
Indications: Simple and complex absence seizures and mixed seizure types

Generic name: **venlafaxine hydrochloride**

Trade name(s): Effexor
Class: phenethylamine monoamine reuptake inhbitor
Type: Antidepressant
Indications: Depression

W

X

Y

Z

Generic name: **zolpidem tartrate**
Trade name(s): Ambien
Class: imidazopyridine
Type: Hypnotic
Indications: Short-term management of insomnia

Chapter 1

BEHAVIOR AND THE CHEMISTRY OF THE BRAIN

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BEHAVIOR AND THE CHEMISTRY OF THE BRAIN

A. HISTORICAL DEVELOPMENTS

Preamble

The birthplace of humanity will be marked not by bones, but by behavior. This is not to belittle the importance of bones; the fossil record will continue to sharpen the focus of our geographic and temporal origins. However, the defining characteristic of Homo sapiens is not the thumb and not the brain case, rather, it is the workings of the brain, the behaviors, the feelings, the mind (if you will).

The interpretation of the geological record goes well beyond physical structure. The skull may be found in proximity to various tools, the bones of animals (perhaps with damage that matches tool structure), plant remains, evidence of households, and so forth. All of this can lead to an educated guess about the culture and behavior of our ancestors. A guess about the function of the brain. Indeed, it is no accident that the term skull is frequently replaced by the term brain case, suggesting that the missing contents are more important than the empty skull. We agree. The purpose of this brief excursion into our ancestry is to provide an extreme example of an old philosophical issue, the mind-body problem (cf., Utall, 1978). Is the mind or behavior of humans a product of the body or is it a separate (spiritual) entity? Nearly all of us are willing to sit on both sides of this philosophical fence:

On the one hand, we are easily convinced that brain cases tell us something about the nature of the contents. Although it is hard to imagine anything less dynamic than a million year old skull ensconced in stone, we believe that this evidence can provide at least a global clue about behavior potential. The surrounding artifacts (tools, etc.) supplement this evidence and enrich our interpretation of the culture of our ancestors.

Paradoxically, as the evidence gets stronger, our beliefs tend to get weaker. Moving forward in time to

our current existence, we have no difficulty accepting the fact that serious brain damage leads to serious changes in behavior. The brain is obviously the organ of (abnormal) behavior. The brain may be recognized as the organ of behavior, but each of us tenaciously hangs onto the belief that we are more than the product of our brain physiology. There is a strong sensation that we have an individual identity (self) and a free will which allows us to control our own brain. Students of the brain and behavior are not immune to these feelings, but the feelings must be suspended on occasion to pursue the fundamental belief that behavior has predictable causes, and that these causes may be found in the workings of the brain.

The purpose of this text is to provide a better understanding of the vehicle for the feelings, emotions, and motivations of the human experience. We will attempt to develop an understanding of the interpenetration of brain, behavior, and environment. We will discuss the chemistry of behavior in both the literal sense of neurochemistry and the figurative sense of an analysis of the reactions with the environment.

Perhaps a word of reassurance is needed concerning the level of analysis that will be pursued. There are three traditional and overlapping subdivisions of the material covered in this textbook:

Neurochemistry is the study of the chemical reactions and functions of the individual neuron or small populations of neurons.

Behavioral Pharmacology is the analysis of the effects of drugs on behavior (usually of animals), with particular emphasis on the development and classification of drugs.

Psychopharmacology is the study of the effects of drugs on behavior (usually of humans), with particular emphasis on changes in mood, emotions, and psychomotor abilities.

Each of these subdisciplines is reductionistic in its own way and tends to analyze the brain and/or behavior in a manner that seems sterile to most beginning students. We do not intend to reduce behavior and chemistry to the simplest level in the way that a chemist would analyze a compound. Indeed, our goal is to synthesize rather than analyze. We intend to further your appreciation by increasing the awareness of the mechanisms of behavior. Connoisseurs of wine are knowledgeable about climate, grapes, and fermentation; they are no less appreciative because they know the vintner's craft. Aficionados of classical music are knowledgeable about tone, rhythm and structure; they are no less appreciative because they know the score. Our goal is to enrich your appreciation of behavior by explaining some of the processes that underlie your feelings.

Enough preambling. Let us trace some of the historical events in both the field and the laboratory that have helped to shape our current conceptualizations of the chemical bases of behavior.

Folk Remedies

The roots of behavioral pharmacology (no pun intended) go back many centuries. A working knowledge of drug use clearly antedates the knowledge that the brain is the organ of behavior, and probably antedates the appearance of the first medical practitioners. In fact, it seems likely that medical practitioners arose as a result of the accumulating knowledge about folk remedies. Those individuals who were especially knowledgeable about the remedies of their culture probably became the medical practitioners. The history of specific drugs will be incorporated in many of the later chapters, but a few examples at this point will provide the flavor of both the power and the complexity of folk medicine. (Several of the specific histories that follow, and numerous additional ones, are presented in more detail in the various editions of Gilman, Goodman & Gilman; e.g., 1980.)

The old adage that one man's cure is another man's poison seems particularly relevant to the history of pharmacology. Many of the compounds that are useful in medicine are derived from arrow poisons, ordeal poisons (to detect practitioners of witchcraft), and pesticides.

A particularly good example of such multiple applications is the use of atropine by the ancient Hindus and Romans. This compound, an extract of the nightshade and related plants, was used as a tool by the professional poisoners of the Middle Ages. At the same time, fashionable women were placing drops of atropine solution into their eyes as a cosmetic. The dilation of the pupils made the women more appealing by causing males to believe they were the object of emotional attraction. These antithetical uses led Linne' to name the shrub Atropos belladonna (Atropos, after one of the three fates, who cut the thread of life; belladonna means beautiful woman.) Today, men and women alike have drops of atropine placed in their eyes, but primarily for the purpose of eye examinations. It is also used for a wide range of medicinal purposes and, as we will see throughout the text, continues to be widely used as a research tool.

An extract from the foxglove plant (Digitalis purpura--the flower looks like a purple finger) was used in an equally diverse fashion. The ancient Romans used digitalis as a tonic, a rat poison, a diuretic, an emetic, an arrow poison and an ordeal poison. More recently, it has been used by more modern physicians for the treatment of dropsy (a vaguely defined anemic disorder) and various disorders of the heart muscle. Amazingly, there is reason to believe that this compound, a stimulant of the sympathetic nervous system, was effective for each of these applications.

Societies that eat mushrooms have known for centuries that some species result in violent illness and possible death, others result in vivid hallucinations, and others are simply a tasty addition to the diet. Claims and counterclaims about which species does what have been handed down through the centuries, but certain species (most notably Amanita muscaria) were well catalogued, and the chemical known as muscarine played a pivotal role in the development of 20th century psychopharmacology.

It is not uncommon for a cure to take on religious significance within a culture. A curious malady of the circulatory system appeared throughout Europe several centuries ago (a few cases still appear). The

disease appeared in epidemic cycles and began as a tingling and loss of sensation in the limbs. As the disease progressed, the circulation of the feet and hands got progressively worse, eventually resulting in gangrene. The blackened limbs would wither away and were said to have been consumed by the Holy Fire. Early stages of the disease could be successfully treated by a sojourn to the shrine of St. Anthony. This remedy was frequently effective, not because of the religious conversion, but because the grain in the area of the shrine was not infected with the ergot fungus that caused the disorder.

One of the best known of the ancient compounds is strychnine, which in addition to its legendary properties as a poison, has been widely used (even by modern physicians) as a stimulant. The compound can be extracted from a wide variety of shrubs and trees (of the genus Strychnos) indigenous to Asia, Africa and Australia. Curiously, the South American relatives of these plants yield a slightly different chemical (curare) that paralyzes the muscles. The latter compound was a very effective arrow poison and is used today as a muscle relaxant during major surgery.

Amidst all of these cures and poisons, almost every culture has managed to find one or more recreational drugs. Coffee and tobacco from the Americas, opium and tea from the Orient, cocaine from Africa, and alcohol from almost everywhere. All of these compounds have been used for their specific ability to change moods and feelings. In some cases, the usage was restricted to ceremonial purposes, but more commonly the use was routine and widespread throughout the culture. We will deal with these compounds in considerably more detail later.

A final example will serve to illustrate the precision that folk medicine can attain within a specific environmental situation. Sickle cell anemia, a genetic disorder of the blood cells, has been a curiosity because this deleterious recessive gene should not be so widespread. In the homozygous condition, in which the afflicted individual possesses both recessive genes, the condition is almost always fatal. However, the heterozygous individual who only has one such gene often shows only mild symptoms of the disease. Why has the sickle cell gene remained in certain populations? The answer lies in the fact that the disorder also confers an advantage in that the individual with sickled cells is much more resistant to malaria, so that in environments where malaria is prevalent, the heterozygous individual is actually better adapted to the environment than an individual who does not carry genes for the disease.

With this part of the puzzle in place, we go on to certain African cultures that raise yams as a primary staple in their diet. The yams are harvested at the beginning of the rainy season, but because of religious proscriptions, are not eaten until the rainy season has ended, at which time a yam feast is scheduled. The curious aspect of this is that there is frequently a shortage of food, and the people endure hunger in the midst of plentiful stores of yams until the rains subside. Although this practice has probably been carried out for centuries, it was only recently discovered (Houston, 1973) that yams contain a compound that combats the sickling of red blood cells. This effect is very desirable except during the rainy season when mosquitoes are spreading malaria. Thus, there emerges an incredibly complex interaction between genetic selection, a seasonal disease, a plant remedy and, holding it all together, a set of behaviors that have assumed the status of a religious custom (cf., Durham, 1982).

The case of the yams exemplifies the grandeur of the interactions of human behavior with the environment. It also serves to place scientific knowledge in perspective. Scientific knowledge does not always add substantively to our practices (knowing that yams reduce sickling does not change their effectiveness). Yet, to the extent that it adds to our understanding, scientific knowledge can greatly increase our appreciation for the functions of the brain. We will now go to the laboratory to see some other stories unfold.

The Unveiling of Chemical Transmission

We have just passed the centenary of one of the major discoveries in brain research. In the 1880's, a controversy was brewing between Camillo Golgi and Ramon y Cajal. Golgi claimed that the nervous system was an interconnected net of protoplasm which, although complicated, was essentially all one piece. The term syncitium was used to describe such a network. Cajal claimed that the nervous system only appeared to be a syncitium and that in reality it was composed of individual cells (neurons) that were so closely juxtaposed that they appeared as a unitary mass.

Looking through the microscope did not resolve the controversy. Nervous tissue is disturbingly translucent and gray in its natural state, thwarting attempts to see cellular detail. The structural details only become apparent when the tissue has been stained with some sort of dye. The ironic ending to this controversy came when Golgi (the syncitium proponent) developed a superb staining procedure that provided enough detailed resolution to prove Cajal was correct. Thus the knowledge that the nervous system consisted of many individual cells, the so-called "neuron doctrine", became the state of the art.

The proof of the neuron doctrine was a double edged sword for students of the brain. On the one hand, this evidence provided a comforting completion to the cell theory of biology; now, all of the organ systems, including the brain, were consistent in structure. On the other hand, an understanding of the function of the brain was complicated by the cellular structure.

The most serious complication involved the electrical activity of nerve cells (see Brazier, 1984, for an intriguing exposition of the history and instrumentation of this era). In the early 1800's, Galvani had formulated his notions of animal electricity when he noticed the twitching of frog legs on a butcher's rack. Based on this and other observations, Helmholtz conducted some clever experiments in the 1850's using reaction time to calculate the velocity at which nerves conduct their electric impulses. He stimulated the sciatic nerve of the leg at two points, one near the hip and one near the knee, and measured the difference in reaction time. He reasoned correctly that the longer latency associated with the location near the knee was attributable to the longer pathway to the brain. His calculations of conduction velocity were amazingly accurate.

The experiments of Galvani, Helmholtz and others clearly demonstrated a role for electrical activity in nervous system function. The problem was that the known laws of electricity required that all the "wires" be connected in a circuit. There was no known mechanism that would allow these tiny signals to leap from one discrete cell to another. The enigma was this: Electrical activity could only work with a

syncitium, but the anatomical evidence showed discrete cells.

A British neurophysiologist, Sir Charles Sherrington, maintained a strong and occasionally outspoken faith that the electrical problems could be solved with more information. With this notion in mind, Sherrington (1906) began a long and exquisite series of experiments to elucidate the electrical activity of the nervous system. His major contribution was in the study of reflex arcs, with special attention to the events that occur when information is transferred from one cell to the next. He coined the term synapse to define the as yet, unseen gap between adjacent (or more accurately, successive) neurons. By making careful measurements of the electrical impulses as they traveled through the reflex arc, he was able to establish the following important principles (refer to Fig. 1-1):

1. Electrical impulses will only pass through a synapse in one direction.

2. There is a constant delay (of about one-half millisecond) between the arrival of an electrical impulse at a synapse and the continuation of the impulse at the other side of the synapse.

3. A volley of impulses arriving at a synapse is not faithfully reproduced on the other side of the synapse (e.g., 3 impulses might result in 0, 1, 3, 5 or some other number of impulses).

4. The arrival of an impulse at a synapse can result either in excitation or inhibition of activity in the cell across the synapse.

Sherrington's experiments were carefully executed, sophisticated, replicable, and at that time, impossible to explain. It is even difficult to devise comparable electronic models today with modern, solid state devices. Yet, Sherrington was confident that convincing electrical explanations would be forthcoming.

At the same time that Sherrington was conducting his experiments (about 1895 to 1920), other investigators were cautiously zeroing in on the relationship between the electrical activity of the nervous system and certain chemical events (see Gilman et al, 1980, Chapter 4 for a thorough historical account. Lewandosky (1898) and Langley (1901) both observed that injections of extracts from the adrenal glands mimicked the effects of electrical stimulation of autonomic nerves. Elliot (1904) made similar observations and proposed that these nerves released an adrenaline-like substance when they were stimulated. (As a graduate student, Elliot was advised that it would be politically dangerous to publish scientific views that contradicted those of Sherrington. He became disillusioned and left science.) A few years later, Dale (1914) noted the similarity between injections of a mushroom extract (muscarine) and the stimulation of the vagus nerve and proposed that this nerve released a muscarine-like chemical when it was stimulated. All of these observations suffered from a common logical flaw: The fact that injections of chemicals mimicked electrical stimulation did not prove that the nerves released these chemicals under natural conditions.

A German investigator, Otto Loewi put the capstone on these chemical theories in 1921. Legend has it

that Loewi's idea for his experiment came to him in a dream, but when he awoke on that Easter Saturday, he was unable to recall the specifics. However, the dream recurred, and on Easter Sunday, Loewi went into his laboratory and performed the experiment that was to prove the notion of chemical neurotransmission and earn him the Nobel Prize. He dissected the heart with attached vagus nerve from a living frog and placed it in a beaker containing a solution of salts to keep it viable (see Fig. 1-2). Then, a second dissected without the vagus nerve and placed into a second beaker. Electrical stimulation of the vagus nerve resulted in slowing of the heart beat (a phenomenon which had been known for many years). The key to Loewi's experiment was that when he pumped fluid from the first beaker into the second, the beating of the second heart slowed down even though there was no nerve attached. The chemical being released from the vagus nerve could be pumped into the fluid of the denervated heart and produce the same effect. Loewi called this chemical Vagusstoff, proving some years later (Loewi & Navratil, 1926) that it was acetylcholine (a muscarine-like compound).

Sherrington and Loewi were not alone in recognizing the importance of the terminal portions of neurons: Claude Bernard had performed a classic series of experiments in 1856 to investigate the properties of curare. British explorers had brought back samples of this curious arrow poison from South America. He dissected the muscle from a frog's leg with the sciatic nerve attached. Stimulation of the nerve would cause the muscle to contract even if the nerve portion were bathed in a curare solution (see Fig. 1-3). If the muscle were immersed in the curare solution, it would not contract via nerve stimulation. But, it would contract when the stimulating electrode was placed directly on the muscle! Finally, Bernard demonstrated an ingenious preparation that involved a ligature (tourniquet) around the leg of an intact frog. Injection of curare caused paralysis of all the muscles except those of the ligatured leg (the blood supply had been cut off by the ligature so the drug could not enter). The key observation was that nerve stimulation in the region of the spinal cord could send impulses into the ligatured leg and cause contraction. Bernard concluded that curare had no effect on the nerve and no effect on the muscle--rather, it acted at the junction between the nerve and the muscle. This clever set of experiments and the prescient conclusion that Bernard reached occurred long before it was even known that the nervous system was comprised of individual neurons, long before Sherrington had described the synapse, and long before it was known that chemical transmission was involved!

B. THE SYNAPSE AND CHEMICAL TRANSMISSION

Basic Principles

The acceptance of the notion of chemical transmission in the early 1900's is a testament to the open-mindedness of the researchers. It was already known that trains of nerve impulses could be transmitted in very rapid succession, in some cases as many as 1000 per second. It required (and still requires) a bold imagination to cope with the notion that discrete chemical events could take place on such a restricted time scale. This section will examine this remarkable process more closely.

The electrical activity of the nervous system is only remotely similar to the electrical activity that occurs

when you turn on the headlights of a car. In a car, the electrical current is carried through the wires by electrons almost instantaneously (at the speed of light) from one side of the battery through the light filament and returning to the other side. The electrical activity is conducted through a complete circuit. In the nervous system, there is no complete circuit and the electrical activity is propagated rather than conducted. This propagation of the electrical activity is much slower than conduction, the maximum being about 100 meters per second.

The source of power for the electrical activity of the nervous system comes from the uneven distribution of charged particles across the membranes of neurons (see Fig. 1-4). (Refer to Ruch et al, 1961, for detailed coverage of basic electrophysiology). The membranes of all of our cells are said to be semipermeable, a characteristic that allows small particles to pass through, while it is progressively more difficult for larger particles to pass through. In the case of neurons, there are large negatively charged particles (anions) trapped inside the cell membrane. The positively charged sodium ion (a cation) is continuously removed from the cell by a biochemical process called the sodium pump. The combination of negatively charged particles on the inside and continuous maintenance of an artificially high concentration of sodium on the outside creates a difference in electrical potential of 70 millivolts across the cell membrane, the inside being negative with respect to the outside. This polarization of charges across the neuronal membrane is termed the resting potential of the cell. Although a difference of less than one tenth of a volt may seem trivial, it must be remembered that this difference occurs across the very thin membrane of a tiny cell. Translated into terms of an electric field, the charge separation is about 10,000 volts per millimeter, and the appearance of 10,000 volts across the diameter of a pencil lead seems a little less trivial!

When an effective stimulus is applied to a neuron, local changes in the membrane take place that allow sodium ions to rush through the membrane (see Fig. 1-5). This influx of positive charge counteracts the negative resting potential and the inside of the cell at this location actually becomes positively charged. The appearance of this local positive charge tends to spread and depolarize the adjacent area of the cell, which causes sodium to rush in at this point, repeating the process. As a result of this movement of charged particles, a wave of electrical activity is observed to travel down the axon. This controlled wave of change in the electrical charge that appears across the cell membrane is called the action potential.

It is important to realize that the electrical action potential is itself a biochemical process. The changes in permeability of the membrane that allow sodium to cross the membrane for a brief period of time require structural changes (usually discussed as opening and closing of channels) rather than the simple movement of charged particles through a medium. Although these changes that are propagated along the axon of the cell are reflected in an electrical signal, it is deceptive to view this as strictly an electrical event. It is a biochemical event that is probably as complicated as the chemical transmission process that follows.

The action potential is a short-lived phenomenon. Upon reaching the terminal portion of the neuron, it is propagated out to the ends of the various branches of the cell (called the terminal boutons) and finally dissipates. The physical gap of the synapse is far too large for this electrical activity to influence the

adjacent cell. (Actually, there are some anatomical situations, called tight junctions, in which the electrical event is passed on directly, but these will not concern us here.)

The arrival of the action potential at a terminal bouton produces yet another change in the cell membrane (see Fig. 1-6). As the action potential dissipates it causes the ejection or release of the relatively large molecules that are stored in the cell terminals. These molecules serve as chemical messengers, (neurotransmitters) and influence the membrane of the next cell. In the most straightforward case, these molecules alter the electrical characteristics of the next cell, setting up a new action potential that is propagated down the next cell where the whole process is repeated. Thus, there is an alternation between the propagated action potential and the translation of this event into the release of neurotransmitter substances. Both events are obviously biochemical processes. Although the terminology is not typically used, it might be conceptually useful to view the first process as chemical propagation to diminish the artificial contrast with chemical transmission.

Major Features of Chemical Transmission

Although Loewi's famous experiment was considered to be convincing evidence of chemical transmission, the formal proof of this process requires that several

logical criteria be met (cf., Fig. 1-7):

1. Synthesis of the Chemical Transmitter

Although the details differ depending on the specific neurotransmitter, each type of neuron has a mechanism to actively and selectively bring precursor molecules from the bloodstream into the cell body. Once inside the cell, these precursor molecules are subjected to a series of enzyme mediated changes, typically being transformed into several intermediate stages before the final product, the neurotransmitter, is formed. Each type of cell contains the specific enzymes that are required for these biosynthetic changes.

2. Transport and Storage of the Transmitter

Most of the metabolic machinery of the cell is localized within the cell body region of the neuron. Since the actual process of chemical transmission occurs at the distal portion of the cell, some mechanism must be present to transport these materials to the axon terminal. There is a rather general flow of protoplasm from the cell body to the terminal portions. In addition to general maintenance functions, the neurotransmitter or intermediate molecules are also carried down the axon.

Once the neurotransmitter or an intermediary has reached the terminal bouton region, another active transport mechanism sequesters the material into small packets called synaptic vesicles. These vesicles serve as both a localized storage facility which also serves to isolate the transmitter substance from other

chemical activity within the cell. This compartmentalization of materials is typical of cellular metabolism in general, and in the case of neurotransmitter control, there may be several stages of storage (called storage pools) for the transmitter substance and various immediate precursors of the transmitter.

3. Release of the Neurotransmitter

This is perhaps the most obvious of the logical requirements for chemical transmission. In order for the information to be relayed from one cell to the next, it is necessary for the action potential to cause the release of the neurotransmitter from its storage vesicles. Although the details of the process remain unexplained, this appears to be accomplished in almost a mechanical manner. The membrane adjacent to a vesicle is physically opened and the contents of one or more vesicles is ejected into the synaptic space. It is this translation of the propagated electrical activity into a physical disruption of the membrane that accounts for the half-millisecond delay that Sherrington observed at the turn of the century.

4. Receptor Sites for the Neurotransmitter

The physical release of the neurotransmitter would be of little consequence if the next neuron had no mechanism to respond to this chemical. In fact, the membrane of the cell across the synapse has specialized regions, called receptor sites, that are chemically compatible with the structure of the specific neurotransmitter that is being released. The most common analogy that has been used to describe this system is that of the lock and key; the neurotransmitter is the key which fits the locks or receptor sites of the next cell.

The complementary nature of the neurotransmitter release and receptor sites suggest that it is more useful to think of a synapse, rather than an individual neuron, as the functional unit. Accordingly, the terminology that has developed designates the cell that releases the transmitter as the presynaptic cell and the cell that responds to the neurotransmitter as the postsynaptic cell.

The functional result of the chemical interaction depends more upon the nature of the receptor site than on the particular neurotransmitter molecule. Normally, we tend to think of systems in the active or excitatory mode, in which case the arrival of the neurotransmitter would result in depolarization of the postsynaptic membrane. If this depolarization is sufficiently strong, it will serve as an effective stimulus for the initiation and propagation of an action potential in the postsynaptic cell.

Contrariwise, the receptor can interpret the arrival of the neurotransmitter in an inhibitory fashion (either via hyperpolarization or stabilization of the membrane potential) and diminish the likelihood that excitatory influences (from other sources) will result in an action potential.

5. Inactivation of the Neurotransmitter

Regardless of whether the neurotransmitter is interpreted in an excitatory or inhibitory fashion, normal

functioning requires some form of inactivation of the effect. Although other types of systems could be imagined, the nature of the nervous system is to encode information in temporal sequences. Thus, a weak stimulus might result in three consecutive action potentials, whereas a strong stimulus might be encoded by twenty more closely spaced action potentials. (Since the size of the action potential is fixed by the nature of the cell membrane and its metabolism, the more obvious solution of encoding by different sized action potentials is not a biological option.) The requirement for sequential transfer of information makes it essential to quickly terminate the effect of the neurotransmitter so that successive releases of neurotransmitter material can result in consecutive action potentials in the postsynaptic cell.

There are two basic types of inactivation that have been identified. One of these is the chemical degradation of the neurotransmitter substance by specific enzymes. Typically, the inactivating enzyme is present in the synaptic cleft and literally removes the neurotransmitter molecule from the synapse by breaking it down into components that are not active at local receptor sites. A second mechanism is a curious phenomenon that has been termed reuptake. The presynaptic cell that releases the transmitter has specialized sites on its own membrane that actively collect the neurotransmitter back into the presynaptic cell. Both of these mechanisms are chemically specific for the neurotransmitter and operate rapidly enough to account for the punctate nature of neuronal function.

C. THE ORGANIZATION AND LOGIC OF CHEMICAL CODING

The Autonomic Nervous System as a Model

If you look into the eyes of your family cat when it is purring on the back of the couch, the pupils will appear as tiny vertical slits. If you help the same cat down from a tree after it has been chased by a dog, the pupils will appear to fill the entire iris of the eye, being virtually round in shape. These differences in pupil size are the result of different forms of chemical transmission, and illustrate one of the most important features of this system, namely, chemical coding of different functions. Two types of fibers from the autonomic nervous system project to the smooth muscles of the eye: One set of fibers utilizes norepinephrine (NE) as the neurotransmitter and is termed sympathetic innervation. The other utilizes acetylcholine (ACh) as the neurotransmitter and is termed parasympathetic (literally meaning beside the sympathetic fibers) innervation.

The smooth muscle fibers that control pupil diameter have two types of receptors: One type of receptor is chemically compatible with the structure of ACh and causes the muscle to contract, thereby constricting the pupil (see Fig. 1-8). The other type of receptor is chemically compatible with NE and inhibits the muscle from contracting, thereby allowing the pupil to dilate. The dual chemical transmitters and dual set of receptors provides for precise control of this system. Furthermore, the system is very efficient by virtue of the fact that a single set of muscles performs a dual function.

This same type of dual control can be observed throughout the autonomic nervous system (see Fig. 1-9).

The rate of the heart beat, the diameter of blood vessels, the peristaltic movement of the intestines, the opening and closing of intestinal valves, salivation and sweating are all under the dual control of the parasympathetic and sympathetic divisions of the autonomic nervous system.

In addition to the somewhat antagonistic effects of ACh and NE, the two divisions are further differentiated by virtue of their anatomy. The parasympathetic division is characterized by discrete fibers that go directly to each of the target organs. Thus, fine adjustments in pupil diameter can occur independently of fine adjustments of peristalsis and salivation.

By contrast, the sympathetic division is anatomically overlapping and tends to operate in a much more global fashion. Thus, during episodes of stress, the changes in heart rate, blood pressure, pupil dilation, sweating, and so forth, all occur simultaneously. Furthermore, the adrenal glands release NE, a closely related compound called epinephrine (E), and dopamine (DA) into the bloodstream. These compounds can then simultaneously infuse into all of the target organs to ensure an even more uniform action.

The autonomic nervous system exemplifies some of the fundamental concepts of nervous system organization and logic. A combination of different neurotransmitters, different receptors, and different anatomical layout provide for a great deal of specificity in response.

Receptor Sites

One of the most common misconceptions when first learning about chemical transmission is to assume that the specificity is inherent in the transmitter substance, e.g., to assume that ACh is excitatory and NE is inhibitory, or vice versa. This is not the case. The different transmitter molecules simply serve as signals and only set the stage for some sort of functional difference, while the actual nature of this difference lies in the type of receptor that is in the membranes of the target organ cells. Thus, a particular neurotransmitter molecule can have effects that are excitatory or inhibitory, depending on the nature of the receptor and the effector cell that the receptor serves.

The control of the urinary bladder provides an excellent illustration of this point (see Fig. 1-10). Most of the time, the bladder function is controlled by a continuing, mild input from the sympathetic nervous system. The release of norepinephrine inhibits the activity of smooth muscles in the wall of the bladder, allowing it to passively fill. At the same time, the smooth muscles that form the sphincter valve are stimulated by the norepinephrine and contract, thereby preventing the leakage of urine from the bladder. The act of urination is under parasympathetic control. The release of acetylcholine stimulates the smooth muscles of the bladder wall, increasing the pressure. At the same time, the release of acetylcholine onto the smooth muscles of the sphincter valve cause it to relax and allow the urine to be expelled. This system is a particularly good example to remember, because it demonstrates both the arbitrary nature of the neurotransmitter signal and the functional interaction of the two divisions of the autonomic nervous system.

Further specificity in chemical transmission can be obtained by having receptors for different portions of

the transmitter molecule. Consider, for example, that the transmitter molecule is shaped like a bird (cf., Fig. 1-11). It would be possible to have a variety of different receptor sites that were shaped like the head, tail, entire top side, or the belly. These different receptor sites for a common transmitter provide utilization of the organism's biochemical resources.

The systems that utilize acetylcholine as a chemical transmitter provide an excellent example of the use of multiple receptors for a single transmitter substance. There are two basic types of receptors for Ach: (a) muscarinic--so named because the compound muscarine mimics ACh at these sites, and (b) nicotinic--so named because nicotine mimics ACh at these sites. The smooth muscles that are target organs of the autonomic nervous system (e.g., pupils, blood vessels, glands, etc.) utilize muscarinic receptors. The striated muscles (e.g, the voluntary muscles of the arm) utilize nicotinic receptors. A slightly different type of nicotinic receptor exists at the autonomic ganglia, which serve as relays for both the sympathetic and parasympathetic divisions of the autonomic nervous system.

Similarly, there are two major types of receptors for NE, called alpha and beta receptors. These receptors respond differently to a variety of different compounds, including the major naturally occurring compounds of the autonomic nervous system, NE (strong alpha and weak beta action) and E (strong beta and weak alpha action). When Ahlquist (1948) first proposed these two receptor types, there was considerable controversy, and Ahlquist correctly asserted that the identification of the receptor type depended on the strength of response to various compounds and not on the direction (excitatory or inhibitory). In most cases, alpha receptors are associated with excitation of the smooth muscles, while beta receptors are inhibitory. However, the muscles of the heart have beta receptors that are excitatory and some of the alpha receptors in the intestines are inhibitory. This exception proves the rule--neither the transmitter substance nor the receptor structure determine the function. The individual cell can, in a sense, use a given type of receptor for any type of function, and NE is very effective for both alpha-excitatory and alpha-inhibitory effects.

Figure 1-12 (also, compare with Figure 1-9) shows a general outline of the autonomic nervous system, which has served as a model for the organization of the nervous system in general. Through a combination of differences in anatomical organization, two neurotransmitter substances, at least two types of receptors for each transmitter, and the option of designating a particular transmitter for either excitatory or inhibitory function, a highly sophisticated set of controls can be obtained. The system is efficient in the use of chemicals, specific in function, and compartmentalized to prevent "spillover" of one function to another.

Chemical Coding of Brain Functions

The organization of the brain is chemically and anatomically far more complicated than the autonomic nervous system. However, the same basic principles of organization apply. A combination of anatomical, neurochemical, and receptor specificity serves to compartmentalize the various behavioral functions of the brain.

There may be several dozen different neurotransmitter substances in the brain, several of which have been studied in considerable detail (cf., Snyder, 1984). The major substances that will be of interest for this textbook are acetylcholine, norepinephrine, serotonin, dopamine, and a class of compounds called peptides. These systems will be treated in considerably more detail as they become relevant in the chapters that follow. For the present purposes, a few selected examples will serve to illustrate some of the principles that we have been discussing.

The hypothalamic region of the brain serves many functions, including feeding and drinking. Anatomical organization can be easily demonstrated by experiments that show excessive eating following damage near the midline of the hypothalamus and a failure to eat following damage near the lateral borders. However, lateral damage impairs drinking as well as eating (cf., Teitelbaum & Epstein, 1962), and it is here that the importance of chemical specificity can be demonstrated see Fig. 1-13). Injections of ACh directly into this region of the brain caused the rats to drink, but had no effect on eating. Conversely, injections of NE caused the rats to eat, but had no effect on drinking (Grossman, 1960). Thus, the presence of two different transmitter substances provide for separate functions within the same anatomical region of the brain in a manner that is directly comparable to the opposing effects of sympathetic and parasympathetic actions on the muscles that control pupil diameter in the cat.

The notion of chemical transmission can be extended to include the various hormones of the endocrine system. We have already seen one example of this in the case of the release of E and NE from the adrenal gland in response to stress. One way of conceptualizing the action of the hormones is to view the entire bloodstream as a single large synapse. The specificity of the hormonal system is determined by the fact that only certain cells (target organs) have receptors that respond to a particular hormone. Although exceptions can be cited, hormonal actions tend to be much longer lasting than neural transmission, and they tend to influence systems in a more global fashion.

In some sense, hormones prepare entire systems for activity or inactivity. Under conditions of emergency, the adrenal gland releases the hormones E and NE to produce a general influence on the target organs of the sympathetic nervous system. Another example can be seen in the case of sexual hormones preparing the seasonal breeder for a whole series of behaviors that occur only during autumn.

It has become very obvious during the past couple of decades that the endocrine system cannot be considered separately from the nervous system proper. The same chemical compound (for example, NE) can be a neurotransmitter when it is released in one manner and a hormone when it is released in another manner. It is simply a special case of chemical control of neural events. Accordingly, the more acceptable terminology is now the neuroendocrine system.

D. INTERACTIONS OF BEHAVIOR, ENVIRONMENT AND BRAIN CHEMISTRY

Convergence of Disciplines

When students of the brain learned that neurons communicate through chemical messengers, the stage was set for developing a new area of inquiry: namely, behavioral pharmacology. This new discipline was based on a simple logic--if the communication system of brain cells is mediated by specific chemicals, then compounds that interact with these chemicals should change the messages.

Consider, for example, that the behavior of drinking when thirsty might be controlled by the release of acetylcholine by certain brain cells. It should be possible to artificially stimulate this system by adding acetylcholine from another source. In the same way that Otto Loewi was able to change the rate of the heart beating in the second beaker, it should be possible to get a non-thirsty animal to drink by administering the appropriate drug. Conversely, it should be possible to prevent a thirsty animal from drinking by giving a drug that blocks the chemical messenger that is being released by the brain cells. These and other more complicated forms of behavior were simply substituted for the physiological test objects (e.g, heart, spleen, pupil, etc.) that were used by Elliot, Dale, Loewi and other pioneers in the field. The experiments worked, and a new area of research was born.

The ability to change behavior by altering brain chemistry underlined the importance of objective analysis of behavior. Behavior is more than a beating heart or a contracting eye muscle, and methods for the reliable observation of behavior were clearly needed. At about the same time that the early experiments in pharmacology were being conducted, a psychologist named B. F. Skinner was formulating a new approach for the study of behavior which he called the analysis of operant behavior. This approach was published in a book entitled Behavior of Organisms (Skinner, 1938)-- a book which became a benchmark in the study of behavior. The basic principles involved the careful control of the animal's environment and the measurements were limited strictly to the observable, objective responses of the animal (e.g, lever presses or key pecks.) Unobservables such as fear, hunger, or thirst were specifically excluded from this system of analysis.

Skinner's system for the objective analysis of behavior was eagerly embraced by the students of the new pharmacology. The precision of the chemically specific transmitter systems could be mirrored by the precision of the operant method of behavioral analysis. The convergence of these two systems became synonymous with behavioral pharmacology, and set forth the basic principle of the discipline: Specific changes in brain chemistry produce specific changes in behavior.

The combination of operant analysis of behavior with pharmacological methods formed a powerful tool for researchers. It is an efficient and effective methodology for the development and screening of new drugs and, to a somewhat lesser extent, for the characterization of drug effects on behavior. But it is not enough. If we are to understand the broader implications of the chemistry of behavior, our considerations must go well beyond the effects of drugs on behavior.

Dynamics of Brain Chemistry and Behavior

Behavior has no clear beginning or end. The analysis of behavior starts out innocently enough to describe the interactions of the organism with the environment. More specifically, it is the interaction of the organism's brain with the environment. The environment includes not only the outside world, but also the organism's internal environment. Of course, the brain is a part of that internal environment and the behavior itself becomes a part of the environment. Lest we become tempted to pursue the logical proof that the universe is made up of behavior, let us return to some more direct issues to illustrate that these considerations are not just idle philosophical musings--we must understand the implications of these interactions in order to appreciate the dynamics of brain chemistry and behavior.

These interactions are presented as six principles for understanding behavioral pharmacology (refer to Fig. 1-14):

Principle 1. Changes in brain chemistry produce changes in behavior.

This is perhaps the most straightforward principle and, as indicated in our previous discussion, the one that has guided most of the research in behavioral pharmacology. Manipulation of the chemical system that controls behavior will change behavior.

Principle 2. Changes in behavior produce changes in brain chemistry.

This principle is a bit more subtle and offers the opportunity to confuse cause and correlation. The fact that behavioral change is correlated with the chemical changes that produced it is simply a restatement of Principle 1. The important point here is that behavioral change can actually produce changes in brain chemistry. One type of change is an increase in the efficiency of the chemical system that produces the behavior (analogous to increased muscle efficiency with exercise). This change may, in turn, produce changes in related chemical systems that were not directly involved in the first bit of behavior.

Principle 3. Changes in the environment produce changes in behavior.

This principle is the simple definition of behavior and requires little in the way of explanation. The major point that needs to be made is that the environment is quite extensive. It includes not only the relationships and contingencies of the external world, but also the internal milieu--blood pressure, gastrointestinal activity, level of energy stores, memory of past experiences, etc. Until recently, the internal environment has been downplayed by the "black box" approach of experimental psychology.

Principle 4. Changes in behavior produce changes in the environment.

In some sense, the only role of behavior is to change the environment. In the simplest case, the behavior is operant and results in opened doors, captured prey, warmed cockles and the like. But just as the environment was expanded in the preceding paragraph, so must our notions of the effects of behavior be expanded to include, for example, changes in the internal environment either directly (as in the case of autonomic responses to a fear arousing situation) or indirectly (as in the case of nutritional changes).

Principle 5. Changes in the environment produce changes in brain chemistry.

We begin to complete the circuit through brain, behavior and environment by noting that environmental changes can produce changes in brain chemistry. In some cases, the environment has tonic influences on brain chemistry as exemplified by responses to seasonal changes, temperature fluctuations, lighting changes and so forth. Other environmental changes are more closely interactive with behavior, and include responses to crowding, members of the opposite sex, complexity of the physical and behavioral environment, etc. These and many other types of environmental manipulations have been shown to alter the status of the neurochemical transmitter systems.

Principle 6. Changes in brain chemistry produce changes in the environment.

On the surface, this seems to be the least likely of the principles. Changes in brain chemistry obviously cannot directly perform operants like opening doors. It can, however, produce significant changes in the internal environment and set the stage for such operants to occur.

The listing of these six principles is a formal way of stating the major considerations that must accompany our study of behavioral pharmacology. We do not recommend that you commit these principles to memory, because individually they represent an artificial analysis of the situation. There is a single statement that embodies all of these principles:

BRAIN CHEMISTRY, BEHAVIOR AND THE ENVIRONMENT

HAVE INTERPENETRATING EFFECTS.

This statement is the major theme of the book, and emphasizes the need to appreciate the complexities of the nervous system. Yes, drugs change behavior. But the effect of a drug can be altered by the organism's behavior, which in turn has been produced by current and past changes in the environment. Drugs do not possess some essence that magically induces a change in behavior. They act through the normal channels of our physiological response to the environment. As human organisms in a complex environment, we are fortunate that these interactions are complicated. As students of behavior, these physiological interactions are pushed to their limits in our feeble attempts to understand them. Do not despair; the thrill is in the pursuit.

E. SUMMARY

Principles

1. The brain is the organ of behavior.

2. Brain functions are controlled by unique interactions between neurotransmitter chemicals and specific receptor sites.

3. Ancient folk medicine and modern pharmacology are both based upon these principles of chemical specificity.

4. The sympathetic and parasympathetic divisions of the autonomic nervous system have served as models for understanding the more complex systems of chemical coding in the brain.

5. Brain chemistry, behavior and the environment have interpenetrating effects.

Terms

acetylcholinesterase

action potential

alpha receptor

anion

atropine

autonomic nervous system

behavioral pharmacology

beta receptor

biosynthesis

cation

chemical transmission

chemical degradation

curare

depolarize

digitalis

ergot

hormone

inactivation

muscarine

muscarinic

neurochemistry

neuron doctrine

neurotransmitter

nicotinic

norepinephrine

operant behavior

parasympathetic

postsynaptic

precursor

presynaptic

psychopharmacology

receptor sites

resting potential

reuptake

semipermeable membrane

storage pools

strychnine

sympathetic

synapse

synaptic vesicle

syncitium

target organ

terminal bouton

Vagusstoff

Chapter 2

GENERAL METHODS OF BRAIN/BEHAVIOR ANALYSES

GENERAL METHODS OF BRAIN/BEHAVIOR

ANALYSES

A. SUBTRACTIVE LOGIC

The Lesion Experiment

The rationale of traditional physiological psychology is based largely on the fact of neuroanatomy. The brains of closely related species have similar appearances, even when viewed in some detail. The brains of different individuals within the same species bear an even more striking similarity-- a fact that has been termed neuronal specificity:

"The location of nerve cells, the trajectory of nerve fibers and the spatial array of synaptic connections are invariant in all individuals of the same species....In this way, the main neuronal circuits achieve an architecture that is breathtaking in its complexity, but frugal in its variability."

(Jacobson & Hunt, 1965, p. 26)

The obvious presence of systematic organization within the brain encouraged the early students of behavior to seek specific relationships between structure and function. The roots of physiological psychology can be traced rather specifically to a series of 19th century experiments by Flourens (1824). By observing the effects of surgical damage, Flourens established the general functions of the spinal cord, the cerebellum, the medulla and the hemispheres. At about the same time, the more detailed physiological studies of Bell and Magendie (ca. 1825) revealed the anatomical and functional distinctions between sensory and motor nerves. Somewhat later, Fritsch and Hitzig (1870) used electrical stimulation techniques to show the important principle of topographical organization, the point-to-point mapping of brain cells and the muscle groups that they serve. The results of these studies were readily accepted, not so much because they were without contradiction, but more because of the Zeitgeist for classification schemes and molecular analysis (cf., the cell theory and developments in chemistry).

All of these experiments were conducted within the framework of the subtractive model of structure/function relationships. The principal method of testing this model is the ablation experiment, which attempts to determine missing behavioral capacities following the surgical removal of specific regions of the nervous system (i.e., the "subtraction" of a portion of the brain to determine which aspect of behavior is missing).

The common sense appeal of the structure function notion probably would have been sufficient to sustain the use of the ablation experiment, but a combination of technological advances and key experimental findings pushed its popularity almost to the point of uncritical acceptance. In 1908, Horsley and Clarke invented the stereotaxic instrument which made it possible to direct surgical damage

to specific structures deep within the brain. In 1939, this instrument was modified for use on the rat (Clarke, 1939), setting the stage for a series of impressive demonstrations of the ablation experiment. Hetherington and Ranson (1940) showed that specific destruction of the ventromedial nucleus of the hypothalamus reproduced the so-called clinical obesity syndrome which, previously, had been associated only very loosely with tumors of the hypothalamus or pituitary gland. Soon it was shown (e. g., Teitelbaum & Stellar, 1954) that specific destruction of the neighboring lateral hypothalamus (less than a millimeter away) resulted not in obesity, but in the rejection of food to the point of starvation.

Thus, the stage was set for at least a quarter century of attempts to relate specific areas of the brain to specific behaviors. During recent years, this method has fallen into disrepute as methods that appear to be more sophisticated have been developed. The problems are not restricted to the technical deficiencies of the lesion method, and we may as well face them now before we go into some of the pharmacological data.

One of the most frequent criticisms of the subtractive logic method is the tendency to ascribe functions to "holes" in the brain. Technically speaking, a lesion in the auditory cortex does not cause a loss of hearing, it is that the remaining portions of the brain cannot mediate the function of hearing. This point of logic seems to be at once subtle and obvious, but the fact remains that errors in interpretation of these experiments are quite likely. The common example of the naysayers is a hypothetical experiment which would first show that a frog will hop when a loud noise is made. This behavior would disappear after removal of the legs. The conclusion: Frogs hear with their legs. The real point to be made here is that this example seems absurd only because we have so much independent knowledge about frog legs and hearing. We would not have this luxury if we attempted to discover, for example, the role of the stria terminalis in eidetic imagery.

There are two major reasons why we should not cavalierly abandon the subtractive model of structure/function relationships and the ablation method of testing this model. The first reason is the simple assertion that function must have a structural basis, and that this structural basis lies within the brain. Specific functions may not be closely tied to obvious structural organization, but in the final analysis, some set of physical structures will be held accountable for behavior.

The second reason for holding onto the subtractive model of determining structure/function relationships is, again, simple and compelling: subtractive logic is the only method available. Flourens did not discover the subtractive model and the ablation method, but rather applied the only tools and logic that the scientific community is willing to use to the specific problem:

(a) an assumption that the universe is lawfully organized (brain structure is related to brain function),

(b) a belief that proximal cause and effect relationships exist (brain structure actually accounts for brain function), and

(c) that cause and effect relationships can be determined by manipulation (changes in structure produce

changes in functions).

Subtractive Logic in Pharmacological Experiments

It is important to realize that pharmacological experiments are a direct extension of the ablation method and subtractive logic. The logic being applied is that if a certain brain transmitter is blocked and certain behaviors change, there is a (chemical) structure/function relationship (refer to Fig. 2-1). All of the more sophisticated chemical interventions (e.g., the mimickers, enzyme blockers, alpha blockers, and others as outlined in chapter 3) are simple variants of this. Some will argue that stimulation experiments (as opposed to lesion or chemical blockade) circumvent these logical problems, but the arguments are less than compelling. A brief review of figure 1-10 will demonstrate the complexities that are involved. Stimulation of the parasympathetic nerve, for example, results in either stimulation or inhibition of the muscle, depending on where one measures the response. Likewise, chemical stimulation with NE results in either stimulation or inhibition of the muscle, depending on where one measures the response. Stimulation experiments are neither simple nor straightforward in their logic, and must be viewed with the same eye for complexity as other experimental approaches.

Even developmental and comparative studies can be characterized by what might be referred to as a receding subtractive model. The logic is based on the fact that young animals that do not have fully developed behavior potential show a common emergence of structure and function, including the emergence of specific pharmacological systems. If time went backward, it would be a lesion study. In fact, the lesion study does occur in nature as time goes forward, with changing behavior as a result of changing structures during senescence. The ablation method, subtractive logic, and the associated problems are pervasive. The effects of alpha-adrenergic blockade, precommissural fornix transection, or the development of olfactory capabilities are no more or no less "messy" than those of Lashley's (1929) classical experiments that attempted to specify the brain mechanisms of intelligence.

The point of all of this discussion is to encourage you to approach the field of behavioral pharmacology with the same squinty-eyed skepticism that has been applied to the old-fashioned lesion methods. It is a relatively new field of inquiry, but only in terms of the procedures. Highly sophisticated approaches and details of neurochemistry do not alter the simple fact that the interpretation of these results is subject to the same pitfalls as the interpretation of brain lesion experiments. And a healthy level of skepticism will lead us to more detailed and accurate accounts of the relationships between drugs and behavior. Let us examine a set of clinical and experimental results that encompass a wide range of anatomical, pharmacological and developmental observations to see how these methods may be applied.

B. BRAIN TRAUMA AND GENETIC "EXPERIMENTS"

Anatomical Destruction

One of the most bizarre cases of accidental brain injury is that of Phinnaeus P. Gage, a railroad worker

(See Bloom et al 1985 for a detailed account). In the Fall of 1848, Gage and his crew were blasting rock. The procedure involved drilling a hole in the rock, then stuffing the hole with alternate layers of packing material and black powder. The packing material was tamped into place with a long steel rod. In a moment of carelessness, Gage apparently tried to tamp the powder layer, and a spark ignited the powder. The resulting explosion transformed the tamping rod into a four-foot projectile which entered Gage's left cheek, passed through the top of his head, and landed several feet away (Fig. 2.2).

To the amazement of Gage's crew, he sat up and began talking to them minutes later and, after a short trip by ox cart ambulance, was able to walk up the stairs to his hotel room. The attending physician determined that his entire index finger could be inserted into Gage's brain case. He placed bandages on the wounds, and followed him through an uneventful period of healing.

Within a few weeks, Gage's physical recovery allowed him to return to his job as foreman. He had no apparent intellectual deficits or memory losses. Yet, his return to work quickly showed the nature of the deficit that follows massive frontal lobe damage. The formerly mild mannered, thoughtful and cooperative foreman had been transformed into a cursing, belligerent tyrant. He lost his job, joined a traveling sideshow for a few years to capitalize (in a small way) on his misfortune, and died of an epilepsy attack about 13 years later.

Phinnaeus P. Gage's tragic case history has become famous in the annals of abnormal psychology as an example of altered behavior resulting from traumatic brain injury. Thousands of other case histories involving trauma, cerebrovascular accidents, tumors and the like have provided parallels to animal experimental data to build up a fairly accurate picture of the functional relationships between anatomy and behavior. Although the effects of such damage are never as simple as one would like, there is nonetheless a certain degree of predictability of motor disturbances, sensory problems, intellectual deficits, emotional disturbances, memory losses, and so forth.

Biochemical Disruption

In the same way that Gage's case history serves as a useful parallel to experimental lesion studies, the disease known as phenylketonuria can serve as a useful parallel to experimental pharmacology (Kaufman, 1975). Phenylketonuria, usually referred to as PKU, is a genetic disorder that appears to follow the simple laws of Mendelian genetics. It is estimated that about 1 in 50 persons is a carrier of the recessive gene for this disorder. When two such carriers have children, there is a 1 in 4 chance that the disorder will be manifested (on the average, 2 in 4 will be carriers; 1 in 4 will be normal). As a result, the incidence of the disorder is about 1 in 10,000 births.

Phenylketonuria appears to result from a disorder of a single gene which controls a single enzyme which transforms the amino acid phenylalanine into another amino acid, tyrosine. When this liver enzyme is missing or seriously deficient, phenylalanine accumulates in the blood, and related metabolites called

phenylketones begin to appear in the urine (hence, phenylketonuria). In the absence of treatment, the prognosis is very bleak indeed. The patients typically show severe mental retardation with an IQ less than 30, abnormalities of posture and reflexes, reduced pigmentation, and a life span that rarely goes beyond 30 years.

The details of this disorder, which are still unfolding, can provide some valuable lessons in the study of brain chemistry. In particular, it serves as a model of the complexity that must be considered in any pharmacological manipulation. The first and perhaps most obvious manifestations of PKU can be attributed to the effects of neurotoxins. In the absence of the critical enzyme, phenylalanine levels rise to about 15 times their normal level and allow large quantities of phenylketones to be produced. These substances may have some direct toxicity to brain cell physiology, but more importantly, they appear to interfere with chemical transmitter systems (Fig. 2.3). A series of different neurochemicals called catecholamines (including norepinephrine, DOPA and dopamine) share tyrosine as a precursor. In the absence of the enzyme, there is less conversion of phenylalanine into tyrosine and deficits in the production of these transmitters may occur. Another way of looking at this is that the PKU deficit makes tyrosine an essential amino acid, since it can only be obtained from dietary sources.

Ironically, the current evidence suggests that this direct effect may be less important in the resulting mental retardation than another, indirect effect. Another essential amino acid, tryptophan, is converted into serotonin (5-HT), an important neurotransmitter of the central nervous system. There is some degree of overlap in the biochemical pathways that convert tyrosine and tryptophan into their respective transmitters. As a result, high concentrations of phenylalanine may inhibit the formation of serotonin. In untreated cases of PKU, serotonin levels are dramatically low. The most successful treatment of PKU is the dietary restriction of phenylalanine which prevents the build up of phenylalanine and related metabolites. This dietary restriction produces a rapid elevation of serotonin levels and halts the progression of the disorder. If such treatment is begun at birth, the major signs of retardation are averted, although some minor difficulties always seem to remain, presumably because of prenatal factors.

The impaired function that results from untreated PKU cases is completely analogous to the case of Phinnaeus P. Gage--it is the result of localized brain damage. In the case of Gage's traumatic lesion, the damage can be localized by an anatomical description. In the case of PKU patients, the damage is localized by a biochemical description, i.e., a biochemical lesion of the serotonin system and, probably, the catecholamines. The important point to remember is that drug effects and transmitter disorders are no more or no less than physical lesions or electrical stimulation.

C. THE ONTOGENY OF BRAIN CHEMISTRY AND BEHAVIOR

Development of Brain Structure

The development of the human brain is nothing less than awe inspiring. Between the time of conception and the time of birth, the full complement of some 100 billion individual neurons are formed, migrating

to their appropriate place within the brain structure. This number is perhaps a little easier to comprehend when one considers that, on the average, a million new brain cells are formed each four minutes between conception and birth! At the time of birth, all of the cells have been formed, but the development of synaptic connections continues, perhaps for 30 or more years in humans. Each neuron communicates with something on the order of 1,000 other neurons and may have anywhere from 1,000 to 10,000 synaptic connections on its surface (10^3 synapses times 10^{11} cells equals 10^{14} synapses with an even more staggering number of possible synaptic interactions.)

The orchestration of all of these connections during the process of development is further complicated by the presence of numerous different chemical transmitter systems. Obviously, our meager abilities to analyze the nervous system can hardly scratch the surface of this process, but we can, nonetheless, gain some general insights into the important events that accompany the development, maturation and ultimate degeneration of the brain.

In the first section of this chapter, we mentioned in passing that the developing brain could be compared to a lesion experiment. Prior to the complete development of the brain, any behavior that occurs must be mediated by the part of the brain that has developed, without the part that is to be developed--exactly as in the case of Phinnaeus P. Gage, whose behavior depended on the remaining brain tissue. If the development of the brain were completely random, the study of developing behavior would provide little information. But to the extent that specific systems may develop in sequence, we may gain some information by looking for parallels between the onset of certain behavioral abilities and the appearance of certain brain systems.

It is important to keep in mind the types of changes that we must look for in the developing brain. Even in the case of human brains, which are relatively immature at the time of birth, all of the cells are present and, to a large extent, in position. This does not mean that the brain is functionally mature at birth. In some cases, the maturation of the biochemical machinery that is necessary for chemical neurotransmission is not completed until some time after birth. Furthermore, the physical complexity of some cells, especially the formation of synapses, may continue for many years after birth. Thus, there is an interdigitation of both anatomical and chemical development.

In general, the increasing anatomical sophistication of the developing brain follows a plan that has been termed encephalization (see Fig. 2-4). The spinal cord and brain stem regions develop and mature at an early age, while midbrain and forebrain regions develop later. The cortex, and particularly the frontal regions, are the last to show fully developed anatomical complexity. These anatomical changes cannot be ignored, but for the present purposes, we will concentrate on the development of neurochemical systems.

Emergence of Behavior and Brain Chemistry

One of the recurrent themes in developmental psychology is that of the emergence of behavior. The term emergence has been used advisedly, because it brings forth the image of something popping to the

surface of a pool, rather than the piecemeal, brick by brick construction of some edifice. Although a case can be made for both types of appearances of behavior, the more remarkable case is that in which the relevant behavior or set of behaviors suddenly appears in full-blown form. A common example of this is the motor skill of walking in human infants. No amount of "training" can teach an infant to walk at age six months, and a complete lack of training does not appreciably retard the age of onset of walking. The "skill" usually emerges within a week or two following the first tentative steps.

We are currently at a very primitive level of understanding the emergence of more complicated, cognitive behaviors. (Unfortunately, the accumulation of this knowledge appears to be more of the ilk of brick by brick construction, rather than some epiphany popping to the surface.) One of the most complete stories that we have available at this point is that involving the neurotransmitter acetylcholine. There are many gaps in the data, but if we are willing to fill these with a bit of conjecture, we can see a coherent example of the parallel emergence of behavior and neurochemical function.

The story began with a theoretical review by Carlton (1963), setting forth the notion that behavioral excitation was under the control of brain systems that use norepinephrine as a neurotransmitter, whereas behavioral inhibition was under the control of brain systems that function through acetylcholine. Accordingly, an increase in activity could result either (a) directly, as a result of stimulation of the norepinephrine system, or (b) indirectly, as a result of blocking the acetylcholinergic system. (We will learn more about the specific drugs later, but for the present purposes a general description will suffice.)

Campbell and associates (1969) extended our understanding of these theoretical notions by studying the development of these behaviors in young rat pups. When rat pups are about 14 days of age, their ears have been opened for only a few days, their eyes are just opening, their fur just barely conceals their skin, and they are very cute. Even at this early age, a significant increase in their activity is produced by drugs that stimulate the catecholamine (norepinephrine and related compounds) systems. By contrast, attempts to increase activity indirectly by blocking acetylcholine functions was to no avail. By 18 to 21 days of age, manipulation of the cholinergic system began to have an effect, and by 28 days of age, the cholinergic blocking effect increased activity in the same way that it does in adults.

The interpretation of these experiments suggests that the brain systems that use acetylcholine as a neurotransmitter are not yet functional in the 14-day old rat. Obviously, drugs that interfere with such a system could not be effective, because there would be no substrate for them to work upon. Once the system has become functional at three to four weeks of age, the drugs have a substrate to work upon and become effective.

It should be noted here that the results of these experiments using a combination of drugs, behavior and age point toward a very specific and testable conclusion: Namely, that a detailed look at the brain should show the maturation of acetylcholinergic cells when rats reach the age of three to four weeks. The results of neurochemical assays (Matthews et al, 1974) provided confirming evidence for the late development of the acetylcholine pathways. Furthermore, related experiments that involved both behavioral and neurochemical assays showed the emergence of brain systems that utilize serotonin as a

transmitter at about 10-12 days of age. Thus, we begin to see a general tendency for the sequential development of systems that can be defined on the basis of the neurotransmitter.

The behavioral functions that are mediated by emerging cholinergic systems appear to be far more complicated than the locomotor activity that was measured in these early experiments. As Carlton suggested in his early review (1963), the cholinergic systems seem to mediate a more general inhibition of behaviors that are non-rewarded or actually punished. Behavioral studies in numerous laboratories, including that of the authors (cf., Hamilton & Timmons, 1979), have buttressed this view, showing that the ability to perform tasks that involve behavioral inhibition do not reach maturity in the rat until about three to four weeks--the same time that the neurochemical systems emerge.

The neurochemical systems must be located somewhere, and this location defines the anatomical basis for these same behaviors. Although the neurochemical systems are somewhat dispersed in the brain, the acetylcholine fibers are heavily concentrated within the limbic system and the forebrain (cf., Feigley & Hamilton, 1971). Literally hundreds of experiments have shown that physical damage to these areas impair the ability of animals to inhibit behaviors that are punished or non-rewarded (cf., McCleary, 1966).

In the case of humans, these inhibitory abilities become very sophisticated and involve such behaviors as inhibiting the attainment of immediate gratification because of complex social contingencies that are likely to be in effect in the future (e.g., not eating the chocolate cake that has been prepared for tomorrow night's birthday party). Interestingly, the inability to meet such exigencies is characteristic of "childish" behavior, and inhibitory control emerges in rudimentary forms at about 4 to 6 years of age. From that point on, the development of these abilities seems to be more gradual, perhaps continuing until about 30 years of age. It is perhaps more than coincidence that the anatomical complexity of the forebrain region shows a concomitant development, and that many of these fibers utilize acetylcholine as the neurotransmitter.

Let us return for a moment to the case of Phinnaeus P. Gage. Despite massive physical trauma to the forebrain, he did not exhibit straightforward deficits in intelligence. Nor did the literally thousands of patients who underwent frontal lobotomies during the unfortunate period of history when these were in vogue--IQ scores typically remained the same or actually increased by a few points (cf., Valenstein, 1973 for related discussion). Thus, man's proudest possession, the big frontal lobes, seem to be minimally involved in intelligence scores. But, they are involved in foresight and the social control of behavior that will have future consequences. This may be the unique feature of humanity, and it may involve to a large extent, the neurons in the limbic system and frontal lobes that function via acetylcholine.

If we follow this line of argument and the associated experimental evidence through adulthood into senescence, the story continues to hold together. One of the emerging characteristics of senility is that of so-called "childish" behavior. A closer examination of these behaviors reveals that it is the failure to take into consideration the future effects of one's behavior upon others--a failure to respond to social

contingencies that require the inhibition of behaviors. It has been known for some time that the aging brain shows selective deterioration of small fibers of the cortex. Evidence from autopsies performed at Johns Hopkins (e.g., Coyle et al, 1983) have shown that the majority of the fibers that deteriorate seem to be those that utilize acetylcholine as the neurotransmitter, especially in the case of Alzheimer's disease.

Thus, the small cholinergic fibers that are the last to appear are also the first to be lost (see Fig. 2-5). The behavioral capacity for complex inhibition is the last to appear and the first to be lost. In the middle, interference with acetylcholine neurochemistry or destruction of the areas where these fibers are concentrated results in impairment of inhibitory behaviors. All of this may be more than coincidental.

We have seen in this chapter some general approaches to the analysis of brain and behavior. We go now to some of the details of the methods that are involved, and will return later to show the application of these details to particular interfaces of behavior and brain chemistry.

D. SUMMARY

Principles

1. All brain research methods, including drug studies, are modeled after the subtractive logic of the lesion experiment.

2. Certain metabolic disorders may interfere specifically with individual neurotransmitter systems.

3. The major neurotransmitter systems mature at differing rates, with the behaviors that are controlled by these systems emerging as cells become functional.

4. Senescence may involve the specific decline of some neurotransmitter systems while others remain more or less intact.

Terms

Ablation experiment

Acetylcholine

Alzheimer's disease

Behavioral inhibition

Catecholamines

DOPA

Dopamine

Encephalization

Neuronal specificity

Norepinephrine

Phenylketonuria

Senescence

Serotonin

Subtractive model

Chapter 3

PSYCHOPHARMACOLOGICAL CONCEPTS

A. ROUTES OF DRUG ENTRY AND EXIT

Drug Administration

Oral administration.

Rectal administration.

Mucous membranes.

Inhalation.

Subcutaneous injection.

Intramuscular injection.

Intravenous injection.

Intraarterial injection.

Intraperitoneal injection.

Transpleural injection.

Intracranial injection.

Intrathecal injection.

Transdermal infusion.

Drug Disposition

PSYCHOPHARMACOLOGICAL CONCEPTS

A. ROUTES OF DRUG ENTRY AND EXIT

Drug Administration

In order for a drug to have an effect, it is necessary for it to reach some specific tissue of the body. The classification of drugs and the description of drug effects is usually based upon the interaction of the drug with this receptor tissue. In the parlance of traditional pharmacology, this interaction at the cellular level is the drug action, whereas the more complicated consequences of this action are termed the drug effect. These terms, action and effect, are frequently used interchangeably, but it is important to recognize that different issues must be considered in each instance.

The basic question that is being addressed here is, "How does the drug get from the shelf to the receptive tissue?" We know from casual experience with pharmaceuticals that drug effects are neither immediate (the headache does not go away at the instant the pill is taken), nor permanent (repeated dosages must be taken). The full consideration of these issues requires a knowledge of membrane biophysics, acid-base kinetics, and other aspects of cell physiology; all of which are of critical importance in the design of pharmaceutical products and in understanding certain aspects of drug actions. Fortunately, we need only consider some of the more global aspects of these topics at this point.

One of the most important determinants of a drug effect is the concentration of drug molecules in the bloodstream or plasma compartment of the body. The drug concentration is determined by the rate of entry into the blood stream and the rate of exit from the bloodstream. In each case, the compound must cross a membrane barrier.

The various membrane surfaces of the body are very similar in terms of their properties that allow

specific types of molecules to pass through them. The membrane can be considered as a double layer of lipid molecules sandwiched between an inner and outer layer of protein molecules (Fig. 3.1). Small membrane pores (about 4-8 Angstroms in diameter) penetrate these layers at intervals along the surface. This physical structure determines the way in which a particular molecule will pass through the membrane:

a. Molecules that are smaller than the diameter of the pores cross the membrane by passive diffusion

b. Molecules that are lipid soluble dissolve in the membrane and diffuse through it according to the concentration gradients.

c. Molecules that are too large and not lipid soluble do not pass through the membrane, except when special metabolic systems called active transport systems carry the molecules through the membrane. Such transport mechanisms are fairly common for endogenous compounds, but do not appear very frequently in the case of pharmaceutical compounds.

There are many different ways in which a drug can be administered, or in terms of the above discussion, different ways to make the drug accessible to the membranes that allow passage into the circulatory system. One way to modify the accessibility of the drug is to change the vehicle, or carrier, of the drug. For example, the drug may be mixed with distilled water, saline, oil, or even solutions of other drugs to systematically change the characteristics of entry into the bloodstream. The rate at which a drug enters the circulatory system varies tremendously, depending upon the route of administration:

Table 3.1

Major Routes of Drug Administration
Oral
Rectal
Mucous membranes
Inhalation
Subcutaneous injection
Transdermal infusion

Intramuscular injection
Intravenous injection
Intraarterial injection
Intraperitoneal injection
Intrathecal injection
Intracranial injection

Each of these routes will be taken up in turn:

Oral administration.

This is certainly the most common method of drug administration, and unless otherwise specified, we assume that taking medication means oral ingestion. This route of administration has the advantage of quickly and easily placing the drug in contact with the relatively large surface membrane of the stomach, which has a rich supply of capillaries for entry into the plasma compartment. The stomach wall is relatively resistant to the irritating properties of most drugs, and the churning action of the stomach will improve the physical distribution of the compound. Finally, the presence or absence of food in the stomach can be manipulated to increase or decrease the rate of absorption, to minimize irritating effects, or to change the chemical environment of the stomach.

There are, however, some special characteristics of the gastric environment that may cause difficulties for the administration of certain drugs. The high acidity of the stomach may alter the structure of the drug, causing it to precipitate and be less easily absorbed. Depending on the acid-base characteristics of the drug, the gastric environment may either increase or decrease the tendency of the drug to split into ionized (or charged) forms. This is a very important consideration for large molecules, because only the non-ionized forms of otherwise lipid soluble compounds will pass through the lipid barrier of the membranes. Because of the differences in pH of the stomach and the intestines, some drugs which are not readily absorbed through the stomach walls because of ionization change their state when they pass from the stomach to the intestine and become lipid soluble. This effectively delays the entry of the drug into the bloodstream. By contrast, other drugs may become ionized and ineffective upon leaving the stomach, so that the amount of the original dosage that actually becomes useful is determined by the length of time it was in the stomach. Modern manufacturing methods now produce several different "time release" formulations that encapsulate the drug into a vehicle that dissolves at some specified rate to release the drug dosage gradually over time.

Rectal administration.

The absorption of drugs administered rectally is essentially the same as that of drugs that reach the

intestine via oral administration. This method is most frequently used under direct medical supervision when it is difficult or impossible for the drug to be administered orally. One of the disadvantages of the method is that the drug may be eliminated before complete absorption has occurred.

Mucous membranes.

There are many drugs that readily pass through the mucous membranes of the mouth and nasal passages. The best known examples of these routes of administration are probably the "nitro" capsules that cardiac patients place under the tongue for almost immediate relief of symptoms, and the snorting of cocaine into the nostrils by users of recreational drugs. In both cases, the drugs are quickly absorbed and significant levels of the drugs enter the bloodstream within seconds.

Inhalation.

Drugs that are volatile can enter the bloodstream very rapidly when inhaled. This is, in fact, just an extension of the mucous membrane route discussed above, but the very large surface area and rich blood supply of the lungs make this an exceptionally rapid route of administration. The major disadvantage is the difficulty of controlling dosage levels, and possible harmful effects upon the membranes. Because of these practical difficulties, this route of administration is usually limited to drugs that are used specifically for their local effects (e.g, anti-asthmatic compounds), and medically supervised anesthesia. It should also be kept it mind that this extremely efficient route of administration renders us vulnerable to the accidental administration of toxic levels of volatile compounds that may be airborne in our environment. Each year, physicians see a number of serious if not fatal cases of poisoning due to exposure to solvents, cleaning fluids, and even the burning of poison ivy along with autumn leaves. On the street drug scene, one of the most dangerous forms of cocaine use is the inhalation of the drug known as "crack". Less acute, but perhaps no less dangerous on a global scale, are the effects of voluntary (and involuntary) inhalation of the contents of tobacco smoke.

Subcutaneous injection.

The skin provides a relatively impermeable barrier to most substances (we will see exceptions later), which led to the development of the hypodermic(literally meaning under the skin) syringe for the administration of drugs through this barrier. When administered in this manner, the drug is sequestered in a localized area, being forced into the interstitial fluid that surrounds the local cells and capillaries. The drug will enter the bloodstream via these local capillaries. Because of the limited physical dispersion of the drug dosage, the absorption of drugs administered subcutaneously tends to be slow and uniform. A further advantage is that the rate of absorption can be controlled by varying the conditions under which the drug is administered. For example, the application of heat or mixing the drug with vasodilators will increase the rate of absorption. More commonly, the physician is interested in slowing down the rate of absorption and may administer the drug in combination with a local vasoconstrictor, mix the drug in an oil vehicle, apply ice over the area of injection, or in emergency situations, even apply a tourniquet between the site of injection and the systemic circulation. Although less commonly

used, it is also possible to surgically implant a capsule under the skin, where the drug is slowly released, sometimes over a period of weeks or months.

Intramuscular injection.

Some drugs have irritant or caustic effects upon local tissues that will cause the skin to sluff off if administered subcutaneously. If the injection route is still preferable, these problems can be minimized by administering drugs deeply into the muscle mass. Certain forms of penicillin are commonly injected via the intramuscular route.

Intravenous injection.

This is the most direct route for the systemic administration of a drug, because it is placed directly into the circulatory system without having to cross any membranes. The rapidity of effects can actually be a disadvantage with this route of administration, since acute overdosage is possible. The most common usage of the intravenous route is the administration of anesthetics, since the level of anesthesia can be carefully titrated by monitoring vital signs. Additionally, drugs that would otherwise be severe irritants to local tissue can sometimes be administered via this route, owing to the resistant nature of the walls of the bloodstream and the rapid dilution of the drug in the moving fluid environment. The self administration of narcotic drugs by this route (sometimes referred to as mainlining) is exceptionally hazardous because of the likelihood of acute overdosage and infections.

Intraarterial injection.

This method also places the drug directly into the bloodstream, but is usually reserved for experimental purposes to inject a drug directly into the blood supply of a specific organ (e.g., the liver or the brain) to assay the effects of the drug upon that organ. One particularly interesting application of this method is to inject a fast acting anesthetic into one of the carotid arteries (see Wada & Rasmussen, 1960). This results in the brief anesthetization of one side of the brain, which can be useful in diagnosing the location of brain functions (e.g., language areas) or disorders such as tumors.

Intraperitoneal injection.

The intraperitoneal route of administration involves the injection of the substance through the wall of the abdomen into the peritoneal cavity. Absorption of the compound occurs largely through the rich vascular bed of the intestines, though from the outside rather than the inside. It is by far the most common method for administering drugs to small experimental animals, owing to the relative difficulty of the intravascular route and the inconsistency of oral administration in laboratory animals. This technique is rarely used in humans because of the potential (though slight) for damaging internal organs and the greater risk of infection.

Transpleural injection.

This is an interesting procedure that occasionally has been used for experimental purposes, especially in small animals. Procedurally, it is somewhat comparable to the intraperitoneal injection, except that the needle is inserted through the rib cage above the diaphragm so that the drug is injected into the pleural cavity. For some drugs, the effect is almost as rapid as an intravenous injection because of the extremely fast absorption through the rich vascular supply of the lungs (hence, the term transpleural, which means across the lungs).

Intracranial injection.

In some cases, it is advantageous to administer a behaviorally active drug more locally into the brain, rather than indirectly through the systemic circulation. There are actually two subdivisions of this route, which overlap to a considerable extent in both theory and practice. The intracisternal route involves the injection of the drug directly into the cerebrospinal fluid (usually abbreviated, *csf*) of the brain ventricles. In some cases, this is done via a cannula (tube) that has been permanently positioned, but in other cases it is done (with skilled hands!) by direct injection through the foramen magnum at the back of the skull of experimental rats or mice. The intracerebral route involves the application of a drug directly onto brain tissue. A common experimental procedure for intracerebral injections involves the permanent placement of a cannula into a specific region of the brain. Minute quantities of drugs can then be administered in either liquid or crystal form to determine the response (both neurophysiological and behavioral) of the specific brain region to a specific drug. These techniques have been very useful as experimental procedures for studying drug effects in experimental settings, but have had limited use in human applications.

Intrathecal injection.

The major application for this route of administration has been the use of the so-called "spinal" anesthetics. In this procedure, a needle is inserted between the vertebrae and through the sheath of the spinal cord. Small quantities of drugs can act on the local cell population and produce anesthesia (usually of the lower body and limbs) while having few if any systemic effects.

Transdermal infusion.

The skin surface normally serves as an effective barrier against the entry of foreign substances into the body. There are, however, some substances that will penetrate the skin and enter the bloodstream. There even have been cases of infant intoxication or death resulting from being wrapped in alcohol soaked bandages as an attempt to reduce fever. (This effect is compounded by inhalation due to rapid breathing of the evaporating alcohol (cf., Arditi & Killner, 1987)). Recently, researchers have been studying the transdermal route of administration for drugs that need to be administered in continuous low dosage over long periods of time (e.g., certain hormones). The drug could be applied on a skin patch, which could be changed every few days or weeks as needed, thereby avoiding the necessity (or inconsistency) of frequent oral or hypodermic administration. There are a number of technical problems in developing this

procedure, the most important of which are the facts that most drugs do not penetrate the skin readily, and compounds that facilitate their entry also may indiscriminately carry other substances (e.g., household chemicals, insecticides, etc.) through the protective barrier of the skin.

Drug Disposition

Getting the drug into the bloodstream is in some sense the easy part of the problem. Once there, the drug faces a morass of physiology which determines the ultimate fate of the compound. The specific action of the drug with the target tissue must be viewed within the much larger context of the distribution of the drug throughout the body.

Table 3.2

Major Routes of Drug Disposition
Protein binding
Liver Enzymes
Renal excretion
Body surface
Pools

Protein binding.

The most immediate consideration is the possibility that the drug will be bound to proteins of the blood (especially, albumin). This binding effectively inactivates the drug by attaching it to a molecule that is too large to reach the target tissue. This usually represents a dynamic equilibrium in which a portion of the drug is bound and a portion may be in the free form. The strength of this binding determines the availability of drug in the free form.

Liver enzymes.

The principle mechanism of transforming drugs from their original form is through the action of enzymes of the liver. Typically, this mechanism is viewed as the degradation and inactivation of the drug; the drug is transformed into other compounds (usually simpler) that are inactive. These compounds are ultimately excreted from the body. In some cases, however, the transformation of the

drug into related compounds results in another compound that may also be effective. This transformed compound may have an action that is similar to the original compound, it may be toxic, or it may have some remotely related effect. In some cases, a knowledge of such transformations allows a drug to be administered in the form of the precursor of the desired compound. In any event, the understanding of a drug action is complicated by the fact that the drug may not stay in its original form.

Renal excretion.

The kidneys form the most common route for the exit of drugs from the body. In some cases, the free form of the drug can be excreted in the urine, while in other cases it is the product of degradation by enzymes. The efficiency of the kidneys in eliminating either the free form of the drug or the active metabolites is an important determinant of drug effects.

Body surface.

In this case, the body surface is considered in a broad sense to include both the skin and the lungs. Detectable quantities of a drug or its metabolites can be found on the skin, especially in the perspiration, but this is rarely a major route of exit. A much more rapid route of exit for some compounds is through the respiratory system. (Despite their location, the lungs are actually a major part of the body's exterior surface.) Significant quantities of some drugs may leave the system along with the water vapor of respiratory exhalation. This forms the basis of the well known breath test for alcoholic intoxication, since the concentration of alcohol in the expired air is closely related to the concentration of alcohol in the bloodstream.

Pools.

The term pools has been applied to the general concept that compounds may exist in several different compartments within the body. For example, some drugs may be distributed in equilibrium throughout the fat stores of the body. The drug that is being stored in this lipid pool is inactive, but serves as a sort of reservoir that can gradually give up its contents to the bloodstream over an extended period of time. Drugs may also be sequestered in the bladder or be chemically bound to certain cellular components. In each case, the amount of drug that is inactivated by the pool, as well as the rate at which the drug can re-enter the plasma compartment (if at all) are important determinants of the overall drug effect.

The Net Effect of Drug Entry and Exit

The existence of multiple routes by which a drug can enter or exit the bloodstream complicates the matter of drug dosage. The attainment of a specific level of drug is not like mixing a solution. It is a dynamic process that involves the entry of the drug into the plasma compartment from several different locations simultaneously and at different rates. No sooner has the drug begun to enter the bloodstream than it begins to leave, again by several simultaneous routes at differing rates. Meanwhile, some of the drug is transformed into other compounds or enters one of several pools from which it may reenter at a

later time. A useful analogy may be to consider the number of spectators who actually are in their seats (receptor sites) in a stadium following an injection of people into the ball park via traffic arteries. The time of arrival is uneven, some people may be sequestered at the concession stands, locker rooms, or the parking lot, some may leave early, and others may leave late. Overall, the effect is predictable, but many factors influence the number of seated spectators at any given time.

In most cases, the combination of all of the mechanisms listed in Tables 3.1 and 3.2 leads to a gradually increasing level of drug in the bloodstream, a stable level for a time, followed by a gradual decline. The duration of each of these phases depends upon the drug, the vehicle, the initial dosage, the route of administration, and the organism's current physiology--a moving target in every sense of the word.

We turn now to some considerations of drug dosage as they interact with behavior.

B. DOSAGE AND BEHAVIOR CONSIDERATIONS

Dose-Response Curves

One of the most important principles of behavioral pharmacology is the concept of the dose-response curve. The simplest and most general expectation would be that larger dosages produce larger effects. Indeed, this is almost always true within some range of the drug dosage, but there is usually some level of dosage beyond which this relationship breaks down, and larger dosages produce progressively less of an effect or even an opposite effect.

An example of this type of dose-response relationship can be seen in Figure 3.2, which shows a schematized change in behavior as a function of various dosages of a drug. Using the same behavioral measure, other drugs would show differently shaped curves at different peak plasma levels. The important point is that the effect of a drug on a behavior cannot be stated in a simple manner: A particular drug may enhance the behavior at low dosages, have no observable effect at some higher dosage, and impair the behavior at still higher dosages. Thus, the appropriate answer to the question, "What does Drug X do to Behavior Y?" is "It depends."

This type of noncommittal answer is (or should be) commonplace in the field of behavioral pharmacology. As shown in Figure 3.3, the plasma concentration of a drug changes continuously over time, as discussed in the previous section of this chapter. If one were to transfer sections of this changing concentration curve to the dose response curve in Figure 3.2, the behavioral effect at any given time would be changing in accordance with the changing concentration curve. In fact, with a single large dosage, it would be possible to show a gradual enhancement of behavior as the drug concentration was increasing, a decline and eventual impairment of behavior as the plasma concentration reached very high levels, a return to enhanced behavior as the drug concentration began to lower, and finally a return to baseline levels as the drug was cleared from the plasma compartment completely. Thus, the effect depends not only on the amount of drug administered, but on the amount of time that has elapsed since

the administration.

Given the interaction of behavior with drug dosage and the dynamic nature of the drug concentration, about the best one can hope for in terms of a stable effect is that shown in Figure 3.4. Properly spaced multiple dosages of a drug can lead to a more or less sinusoidal variation in plasma concentrations within the range of dosage that has the desired behavioral effect.

Law of Initial Values

The law of initial values was put forth many years ago during the early stages of studying the cardiovascular system. It was noted that certain drugs which reduced a rapid heart rate had no effect on the normal heart or one which was already beating slowly. Likewise, drugs that raised an abnormally low heart rate were ineffective in raising the rate of a normal heart or one which was already beating rapidly. Thus, the effect of a drug depends upon the initial value of the heart rate.

This same principle can be applied in many cases of the behavioral effects of drugs. As shown in Figure 3.5, behaviors that have a moderate baseline respond in the typical dose-dependant manner; an increase at moderate dosages and a progressive decline at higher dosage levels. Behavior that begins at high levels is less effected by low dosages and the first effect that is observed is a decline in the rate. At lower baselines, the drug-induced increase continues into higher dosage ranges before declining.

The law of initial values, as it applies to behavior, is frequently referred to as a rate dependency effect. That is, the effect of a drug depends upon the rate of behavior that is observed at the time the drug is administered. These principles certainly do not apply to all drugs, but the phenomenon is sufficiently common to make it necessary to consider the possibility whenever a new drug and behavior combination is tested.

The law of initial values interacts in a complex fashion with the concept of dose-response effects. In some sense, it is possible to hold the plasma level of a drug constant and vary the "dosage" of behavior (low, moderate, or high) that is used to assay the effects of the drug. Furthermore, there is very likely a dynamic interaction between the baseline behavior and the drug-altered behavior in that a higher rate of behavior (induced by the drug) might be less influenced by the drug.

Drugs Have Multiple Effects

It is almost a truism that every drug has multiple effects. Ideally, a drug would have only one effect, which could be used for a specific therapeutic purpose. More commonly, any given drug may have several major effects and several minor effects. As an example, a particular drug may be given as a muscle relaxant, but have a "side effect" of producing drowsiness. The same compound may be prescribed for another patient for the purpose of producing drowsiness and lowered anxiety, with a side effect of muscle relaxation. Along with these major effects, several minor side-effects might be common

to both prescriptions and include cardiovascular problems, gastrointestinal upset, skin rashes, and so forth. In general, the higher the dosage, the greater the number of different drug effects.

Each of these effects and side effects may have a different dose-response curve. As a result, a typical situation might be that shown in Figure 3.6, in which a dosage prescribed for Effect A might have Side-Effect C. A dosage prescribed for Effect B would be would have Side Effects C and D, as well as the tail end of Effect A, which is labeled Side Effect E. This sort of entanglement of desired effects and side effects prevents many drugs from being marketed.

These considerations are especially important in trying to unravel the effects of a drug upon complex behavior. Consider, for example, a situation in which an animal is performing a visual discrimination that enables it to obtain food and avoid shock according to a variable interval schedule. A particular drug would very likely influence each aspect of the task (e.g., visual perception, hunger, pain threshold, memory, etc.) at differing dosages, and the rate of behavior engendered by task parameters would, in turn, interact with the drug dosage. Thus, many different combinations of observations must be made before a complete account can be given.

A specific set of examples may help to understand some of the dynamics of these dose-response curves, multiple effects, and other complications of interpretation (refer to Fig. 3-7).

Low doses of epinephrine produce a slight drop in blood pressure, whereas high doses produce a large increase in blood pressure. This curious reversal of effects can be explained as follows: The molecular structure of epinephrine allows it to interact with both alpha and beta receptors. The beta receptors, although fewer in number, are more sensitive than the alpha receptors. With *low* dosages of epinephrine, the *beta* receptors are the only ones effected and they inhibit the smooth muscles of the blood vessels causing a decrease in the pressure through vasodilation. *High* doses of epinephrine stimulate *alpha* receptors, which cause the constriction of blood vessels and a corresponding increase in blood pressure. The beta receptors are also stimulated, but their influence is overpowered by the effects of the alpha receptors. (Careful observation will show a brief reduction of blood pressure as the epinephrine first enters the system and as it is finally leaving the system, reflecting the low concentrations of the drug at these times.)

Almost exactly the same type of change in blood pressure can be observed with low and high doses of acetylcholine, but for different reasons. *Low* doses of acetylcholine reduce the blood pressure by acting on the *muscarinic* receptors which inhibit the smooth muscles of the blood vessels to cause vasodilation. *High* doses of acetylcholine produce a large increase in blood pressure by stimulating the *nicotinic* receptors of the autonomic ganglia (refer also to Fig. 1-9 and Fig. 1-12). These nicotinic receptors are much less sensitive to circulating levels of acetylcholine, but once stimulated, their effects are much more potent than those of the muscarinic stimulation. Under these conditions, the *sympathetic ganglia* predominate, and the resulting stimulation of the adrenal gland and release of norepinephrine from the sympathetic fibers cause an increase in blood pressure. Thus, the large dose of acetylcholine increases blood pressure indirectly via sympathetic arousal.

In these examples, we see the essence of dos-response interactions. Two completely different drugs (epinephrine and acetylcholine) produce identical profiles of change in blood pressure (a decrease at low doses and an increase at high doses.) In each instance, the reversal occurs because low doses influence one type of receptor while high doses influence a different type of receptor. Furthermore, in the case of acetylcholine, the final effect is actually due to the indirect activation of an opposing system. This particular set of results makes sense because the underlying mechanisms have already been determined. In many cases of drug and behavior interactions we do not yet enjoy this luxury.

Individual Differences in Drug Effects

The effectiveness of specific drugs can also be influenced by a wide range of organismic variables such as species, age, sex, disease status and behavioral history. In many cases, the specific origin of these differences in drug response cannot be identified, but some general comments can be made in relation to the dosage considerations discussed above. The notation of such variables as age, sex, species, and so forth does not describe the underlying cause of differences in drug response, but is rather used as a convenient label for sub-populations that may share some common physiological variable.

One of the most important physiological differences that interacts with the behavioral effects of drugs is the neurochemical status of the brain. There are well documented changes in brain chemistry during the course of development and continuing through senescence. The presence or absence of sex hormones, the environment of the organism, and the behavior that the organism engages in can all modulate these neurochemical changes. Since most of the behaviorally active drugs produce their effects through interaction with these chemical substrates, the variables that alter neurochemistry interact with drug response. It is simply easier and more convenient to specify some external variable such as age or sex, rather than attempting to outline the more directly relevant neurochemical factors.

Differences in drug response can also occur in the absence of any important differences in the neurochemical substrates. All of the ports of entry into and exit from the bloodstream vary as a function of these external variables. For example, liver function is not fully developed in the very young and no longer fully efficient in the very old. Differences in behavioral and dietary history will alter liver function, gastrointestinal function, cardiovascular efficiency and general metabolism. Body fat levels vary in response to a wide range of variables. Each of these changes has the capacity to alter the drug response through a simple shift in the time course of effective drug concentration in the bloodstream. The same relative quantity of drug might produce an increase in the behavior of a young organism, no change in adult females, and an impairment of behavior in aging males. As indicated before, "It depends."

Calculating Drug Dosages

At some point, all of these considerations of the dynamics of drug dosage must yield to a pragmatic decision. A specific dosage must be administered to a specific organism. In some sense, this involves

adding enough drug to the organism's system to produce the desired concentration in a volume of liquid, the blood plasma. Since the volume of the plasma compartment is highly correlated with body weight, dosages are usually measured in milligrams of drug per kilogram of body weight (mg/kg). In the case of experimental animals, this is usually done precisely for each animal. In the case of humans who are taking pills or capsules, dosages are commonly based on average size.

Drugs differ markedly in the actual amount that is effective, ranging from millionths of a gram up to several hundred milligrams. Perhaps the most important bit of information about a particular drug is the smallest dosage that will produce a desired effect. This measure has been termed the minimum effective dosage (MED) and is usually determined empirically by administering varying dosages to a test population to calculate the minimum dosage that is effective in 50 percent of the population, the MED-50 (sometimes it is simply referred to as the ED-50). Since most drugs have the potential for lethal effects at high dosages, a second measure is calculated for the lethal dosage for 50 percent of the population, the LD-50. A safe drug is one which has a lethal dosage that is several times larger (preferably 10 or more) than the effective dose. This therapeutic ratio (LD-50/MED-50) represents the clinical safety factor of a drug. This ratio is not specific to a drug, but rather to a drug effect: A drug, for example, might have a safe ratio for use in anxiety reduction, but be dangerous in the dosage required for muscle relaxation.

C. THE BLOOD BRAIN BARRIER

All of the preceding discussion of the dynamics of drug dosage has dealt with the general concepts of the passage of drugs between the bloodstream and the tissues. Although these general principles continue to apply, behaviorally active compounds require special consideration because of some of the unique physiological aspects of the brain. In particular, the vascular system of the brain is both quantitatively and qualitatively unique.

The brain is one of the most richly vascularized organs of the body. The two internal carotids and two vertebral arteries (which supply all the blood to the brain) branch out into an extremely dense system of capillaries. Consequently, the brain is responsible for nearly twenty percent of the body's total oxygen consumption, even though it accounts for less than two percent of the body mass. Neurons are particularly vulnerable to ischemia, and such a lack of blood flow for as little as four to five minutes can lead to serious brain damage.

Ordinarily, organs that are highly vascularized receive a disproportionate share of a circulating drug, because the rate of equilibration of drug levels in the plasma and the adjacent tissue is directly related to the rate of blood flow. However, the dense capillary system of the brain is very selective in terms of the molecules that will pass through into the surrounding tissue space. Water, oxygen, carbon dioxide pass freely through the endothelial walls. Glucose, which supplies virtually all of the nutritive requirements of brain tissue, also passes through relatively freely. Thus, there is an efficient exchange of molecules that are essential for the high metabolic demands of neural tissue.

The story is quite different for other types of molecules. The capillaries of the brain have two special features that tend to prevent the passage of molecules into the adjacent tissue space. The endothelial cells that form the walls of the capillaries are densely packed, such that only small molecules can pass through the junctions. Additionally, glial cells called astrocytes surround about 85% of the surface of the capillaries, adding a lipid barrier to the system. Thus, large molecules and molecules that are not lipid soluble do not easily penetrate the brain. These special features of the cerebral vascular system have been termed the blood-brain barrier.

Another special feature of the central nervous system is the cerebrospinal fluid (csf) which fills the ventricles of the brain and central canal of the spinal cord. The csf is formed by blood vessels within the ventricular system, most notably the concentrated groups in the lateral ventricles which are termed the choroid plexus. The csf excreted by these vessels is similar to blood plasma, except for very low levels of proteins and cholesterol. It is the extracellular fluid of the brain, which is formed continuously and absorbed (by the arachnoid villi) at a rate of about 10% per hour. Thus there is a continual flow of the fluid which bathes the brain cells. The capillary walls of the choroid plexus have the same dense epithelial structure as those within the brain tissue proper, hence provide an extension of the blood-brain barrier.

The blood-brain barrier should not be viewed as a system which isolates the brain, but rather as one which buffers it from the changing conditions of the remainder of the body (see Fig. 3.8). The critically important ions that determine the electrical excitability of neurons (Na^+, K^+, Ca^{++}, and Cl^-) equilibrate with the brain fluids very slowly, requiring as much as 30 times longer than in other tissues. Relatively small molecules such as urea are exchanged rather freely with muscle tissue and other body organs, but enter the brain very slowly over a period of several hours. Larger molecules such as bile salts and circulating catecholamines (from the adrenal glands and peripheral autonomic nervous system) are essentially blocked from entering the brain. (However, the acidic precursors of brain transmitter amines such as L-DOPA and 5-hydroxy tryptophan enter readily.) Thus, the brain is protected from fluctuations of chemicals in the plasma compartment, allowing homeostatic processes a considerable margin of time to correct any deviations while the brain's environment remains relatively constant.

The physiological paradox that arises is that a buffer system between the fluctuating physiology of the organism and the brain also buffers the information that the brain must use to guide the correction of the homeostatic deviations. This paradox has apparently been resolved by the presence of a group of structures called the circumventricular organs. As the name implies, these organs lie adjacent to the ventricular system of the brain and more importantly, lie outside the blood brain barrier. There are five such organs, each of which appears to have specific chemical receptors to monitor changing body conditions and relay the information to other areas of the brain: The subcommissural organ and subfornical organ are responsive to levels of angiotensin and plasma volume, respectively, and are important in the regulation of thirst for the maintenance of body water and electrolyte balance. The posterior pituitary is responsive to a variety of pituitary, adrenal, gonadal and hypothalamic hormones, and helps to regulate the circulating levels of all of these. The pineal gland is involved in circadian

rhythms. The functional importance of the supraoptic crest is uncertain.

The nature of the blood brain barrier poses a number of problems in terms of the behavioral response to drugs. In the most extreme cases, some compounds simply do not enter the brain in significant concentrations. In other cases (e.g., dopamine or serotonin), the relevant compound per se does not enter, but the precursor molecules can be administered to facilitate the synthesis of the active form within the brain. The compounds can also be injected directly into the brain or CSF, physically bypassing the barrier, but several compounds have so called paradoxical effects on brain tissue. For example, penicillin produces convulsions, epinephrine in the ventricles leads to somnolence, and curare can lead to seizures. Aside from some general guidelines relating to molecular size and lipid solubility, it is difficult to predict with accuracy how easily a drug will penetrate the brain and what the effect will be. In many cases, it is necessary to make an empirical determination.

A more subtle aspect of the blood brain barrier is that it is differentially effective in different areas of the brain. The white regions of the brain are composed mainly of fibers, which are surrounded by glial cells to form the myelin sheaths. As a result of this additional lipid barrier, these regions of the brain reach equilibrium with certain drugs much more slowly than the cellular regions of grey cortex. To the extent that these different areas serve different behavioral functions or are differentially sensitive to the drug, the overall response to a drug dosage over time will become increasingly complicated.

Finally, the blood brain barrier changes as a function of organismic variables, the most important of which is probably age. The myelinization of fibers appears late in the course of ontogenetic development. Consequently, young organisms are frequently responsive to drugs that are ineffective in adults. Furthermore, the completion of the process of myelinization is not uniform throughout the brain, so that organisms of different ages would have different concentrations of drug in certain brain areas that were not fully myelinated.

On the bright side, the blood brain barrier can be a useful stage for certain types of experiments. One of the best known is that involving drugs that block the acetylcholine receptor. The systemic administration of such compounds (e.g, atropine or scopolamine) influences not only the brain, but also the entire parasympathetic division of the autonomic nervous system. Are the resulting effects due to brain actions or the effect upon the peripheral system? The addition of a methyl group onto the nitrogen of these compounds (methyl atropine or methyl scopolamine) forms a compound that is very similar in terms of its effects in the periphery, but it will not cross the blood brain barrier. Thus, if the centrally active form produces an effect that the methylated form does not, a reasonable conclusion is that the effect is caused by the action of the drug on the brain.

D. CLASSIFICATION OF DRUGS

Methods of Classification

One of the most important contributions of the scientific method is that of classification. Through the

process of classification, chaos turns into order and mountains of individual facts turn into simple concepts. As examples, we have the organization of plants and animals into an organized system that defines genera, orders, families and species of animals. We have the periodic table that organizes elements on the basis of their subatomic structure. In each case, the classification results in a system that both facilitates memory and increases our understanding of the interrelationships among the various subcategories--the concepts of mammals and heavy metals provide insights that might not be apparent from the particular examples of llama and lead.

The goal of the field of behavioral pharmacology is to organize and classify behavior and drugs into systems that will enhance our understanding of the relationships between chemistry and behavior. At the present state of development of this discipline, there are numerous schemes for organizing the available information, and none of these is as discrete and well organized as the systems for organizing chemical elements and species. An additional hundred years or so of research will certainly improve this situation, but we already have some useful systems of classification that guide our research efforts and our thinking in this area.

There are three major methods of classifying drugs: (a) behavioral, (b) biochemical, and (c) structural. Table 3.3 shows a few representative selections for each type of classification. This table is by no means exhaustive, but simply shows the types of considerations that go into each scheme of classification.

Table 3.3

Drugs Classified by Molecular Structure	Drugs Classified by Biochemical Actions	Drugs Classified by Behavioral Effects
amino acids	receptor blockers	stimulants
monoamines	mimickers	sedatives
benzodiazepines	synthesis inhibitors	hallucinogens
alcohols	false transmitters	antidepressants

Behavioral categories.

The classification that we are most interested in is that involving the behavioral effect of the drug. Drugs are administered to produce some alteration in behavior (or physiology) such as increasing arousal level, combating depression, lowering blood pressure, and so on. As information about the effect of each particular compound becomes available, the name of the drug can be added to the list pertaining to each

desired effect.

This method of classifying drugs by their behavioral action is probably the oldest method used. As indicated in Chapter 1, early practitioners discovered various herbs and chemical preparations that produced specific effects. This method has limitations, however, in that the categories that define behavioral change may not always be sufficiently specific and any particular compound may have several different effects.

Biochemical categories.

An alternative scheme of classification is to determine the biochemical effects of the drugs. That is, the drug action rather than the drug effect. This is probably the most highly sophisticated scheme of classifying various drugs, and deserves some additional amplification at this point.

The headings in the biochemical scheme of classification are based on the mechanisms of chemical neurotransmission. A typical way or organizing the information is in terms of drugs that either impair or facilitate the action of a particular neurotransmitter system. Let us consider some of the logical possibilities for changing the function of a particular transmitter system (refer to Fig. 3.9):

a. Precursor compounds

In some cases, the amount of transmitter substance that is synthesized and stored for later release may be increased by injecting additional precursor molecules.

b. Synthesis blockade

A drug may interfere with the enzymes of synthesis (Es), reducing the amount of transmitter substance that is available for release.

c. Transmitter depletion

A drug may cause the gradual and continual leakage of transmitter substance from the vesicles, resulting in an exhaustion of the transmitter stores.

d. Prevention of release

A drug may interfere with the release of transmitter that normally occurs when an action potential arrives at the terminal bouton.

e. Receptor inhibition

A drug may have chemical characteristics that allow it to occupy the receptor sites and prevent the normal transmitter substance from acting. This can occur in two separate ways: Some drug molecules occupy the receptors in a reversible manner, and simply compete with the real transmitter molecules for access to the receptors (competitive inhibition). Other drug molecules may alter the physical shape of the receptor so that the real transmitter no longer fits, thereby reducing the total number of functioning receptor sites (noncompetitive inhibition).

f. Mimicking

A drug may have chemical characteristics that allow it to occupy the receptor sites and stimulate the postsynaptic membrane in a manner comparable to that of the naturally occurring transmitter.

g. Inactivation blockade

A drug may interfere with the enzymes that normally degrade the transmitter substance (Ed). In low dosages, this can increase function, but if the accumulation of transmitter is too great, the continuous stimulation can actually block function by preventing repeated action potentials.

h. Reuptake blockade

This is functionally equivalent to item g above, but occurs in those systems in which the transmitter is inactivated by the process of re-uptake rather than enzyme degradation.

i. False transmitters (-)

A drug may be taken up by the cell, stored in the vesicles, and released along with normal transmitter during normal stimulation. To the extent that the drug molecules are less effective, or actually block receptors, the level of function will be reduced.

j. False transmitters (+)

This is identical to item i, except that some drugs may be more effective than the naturally occurring transmitter and increase the level of function upon release.

k. Conduction blockade

Some drugs may prevent the action potential from being conducted down the axon to the terminal bouton. In these cases, the entire synaptic region may be functionally normal, but is rendered nonfunctional because stimulation cannot occur. These drugs are usually not specific to a particular transmitter system, but are more likely to be selective in terms of metabolic properties, as in the case of some local anesthetics that influence primarily fibers of small size.

As indicated in earlier sections, most drugs have multiple behavioral effects which may be due to multiple biochemical actions. Drug dosage would interact in a complex fashion with neuronal function in those cases, for example, in which low levels of the drug blocked re-uptake while higher levels also mimicked the real transmitter. Also, as indicated in items f, g and h above, excessive stimulation can result in a functional blockade.

Structural categories.

The third column in Table 3.3 includes categories that are based strictly on the molecular structure of the drugs. This column by itself provides no information at all about either the biochemical action of the drug or the behavioral (physiological) effect of the drug. As we will see below, it becomes useful only when used in the context of the other two columns.

Categories are Useful in Understanding Drug Effects

Therapeutically, the second and third columns of Table 3.3 are completely irrelevant. It would be possible to list the names (or numbers, for that matter) of compounds that are known to have each desired behavioral effect. The drugs could be prescribed solely on the bases of their effects and nothing more need be known. Indeed, this accounts for a large portion of day-to-day therapeutic decisions. Yet, it is an unsatisfactory (and potentially dangerous) state of affairs if this is done in the absence of an understanding of how the drugs interact with the brain and behavior. We will now examine more carefully the progression from a simple, pragmatic practice of therapeutics to a more fundamental understanding of the drug interactions with the brain and behavior.

The complexity of understanding drug effects arises from the fact that any drug produces multiple changes in behavior and different drugs may produce similar changes in behavior. For example, Drug A may reduce depression and also cause tremor. Drug B may be equally effective in reducing depression, but also cause drowsiness. Why?

The answer to this question must be sought at another level of analysis. Typically, researchers would determine the relationship between the biochemical actions of Drug A and Drug B. If both drugs interfere with the reuptake of Transmitter X, then one can postulate that Transmitter X may be the basis for the mutual effect of combating depression.

A test of this postulation might involve moving over to the third column of Table 3.3 to compare the molecular structure of Drug A and Drug B. If these compounds are similar in structure, then additional compounds (Drug C and Drug D) may be synthesized and administered to determine their behavioral effects on depression and their biochemical actions on Transmitter X.

Figure 3.10 schematizes this procedure of interrelating molecular structure, biochemical activity and behavioral effect. This process forms the basis for all of our research and can sometimes lead to a

relatively complete understanding of the chemical bases of behavior. For example, an entire group of compounds may differ only in terms of the length of the carbon chain that is attached to a common triple-ring structure. If the effectiveness of these compounds in blocking the reuptake of Transmitter X is related to the length of this side chain, then something has been learned about the biochemical specificity of this reuptake mechanism.

This type of information is called the structure-activity relationship and has been determined for a number of different systems as will be seen throughout the text. For example if the same compounds that are most effective in blocking reuptake are also most effective in combating depression, then it seems likely that depression may be related to the level of functioning of this particular transmitter system. Additional compounds (e.g., compounds that mimic the transmitter or increase the synthesis) may be studied to further evaluate the hypothesis. The resulting description of the relationship between drug and behavior is far more useful than a simple catalogue of drugs and drug effects.

We have examined some of the basic principles for the organization of the brain and behavior, some of the considerations that go into the study of drug effects, and some of the considerations that go into classifying drugs for purpose of therapeutics and research. The next section of the text will study specific areas in which these principles have been especially useful in furthering our understanding of the chemical bases of behavior.

E. SUMMARY

Principles

1. Drug molecules must reach the appropriate target tissues before they can become effective.

2. The accessibility of the drug molecules to the target tissue is largely determined by the amount of drug in the bloodstream.

3. Drug molecules may be injected directly into the bloodstream, but they are more commonly administered by indirect routes such as oral ingestion.

4. Once the drug has been administered, a host of physiological factors determine the how fast the drug molecules enter and exit the bloodstream.

5. Different dosages of a drug change not only the magnitude of the drug effect, but also the nature of the drug effect.

6. All drugs have multiple effects, and the term side effect is usually applied to an effect that is not

desired.

7. Individual differences such as behavior, gender, age and general health status all influence the effectiveness of a drug.

8. The blood brain barrier provides a buffer between the central nervous system and the remainder of the organism's physiology.

9. The classification of drugs according to biochemical actions and molecular structure contributes to the development of new drugs and a better understanding of the chemistry of behavior.

Terms

Active transport

Astrocytes

Blood-brain barrier

Body surface

Cerebrospinal fluid

Choroid plexus

Circumventricular organs

Competitive inhibition

Dose-response curve

Drug action

Drug effect

False transmitter (+/-)

Hypodermic

Inhalation

Interstitial fluid

Intraarterial

Intracerebral

Intracisternal

Intracranial

Intraperitoneal

Intrathecal

Intravenous

Ischemia

Law of initial values

LD-50

Lipid soluble

Liver enzymes

MED-50

Membrane pores

Mucous membranes

Noncompetitive inhibition

Oral

Organismic variables

Pools

Precursor

Protein binding

Rate dependency

Rectal

Renal excretion

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Structure-activity relationship

Subcutaneous

Therapeutic ratio

Transdermal

transpleural

vehicle

Chapter 4

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SPECIFIC FEARS, VAGUE ANXIETIES AND THE AUTONOMIC NERVOUS SYSTEM

A. INTRODUCTION

Fear is one of the most pervasive and pernicious of human conditions. At low levels, it is a frequent contributor to normal activities, providing both energy and direction to our interactions with the physical and social environments. In its clinical manifestations, fear contributes to a variety of psychiatric disorders including phobias, compulsions, panic attacks, and anxieties both specific and vague. It is the cornerstone for mental distress which leads to a long (and growing) list of psychosomatic disorders such as hypertension, headache, ulcers, cardiovascular disease, and immunological dysfunction--to name a few. We would do well to further our understanding of fear and anxiety. The goal of this chapter is to interrelate: (a) the environmental conditions that lead to various states of fear, (b) the changes in the

central and autonomic nervous systems that accompany these environmental conditions, and (c) the pharmacological interventions that are available for research and therapy.

The term fear is firmly entrenched in both our technical vocabulary and the vernacular. It would serve little purpose to offer a precise definition for the present discussion, but some consideration of the ways in which the term has been defined may be useful. For research purposes, conditioned fear typically is defined operationally in terms of the environmental events that set the conditions for fear, although some behavioral or physiological index is frequently used to corroborate the effect. Irrespective of the precision of this operational definition, the ultimate goal of the research (and, indeed, the choice of parameters that make up the operational definition) is to provide an experimental model that parallels the human conditions listed above. This remains a distant goal, but major developments within the areas of experimental psychology and psychopharmacology allow a reasonably coherent model to be presented.

The terms conditioned fear or learned fear underscore the importance of experience in determining the sources of fear. Some theorists claim that all fears are learned during the lifetime of the individual. Even those who argue for innate fears present a very short list of exemplars (e.g, fear of snakes, fear of unsupported heights). In virtually all cases, the fear is based upon some consistent relationship between the environment and some painful or otherwise noxious stimulus. It is the understanding of these environmental relationships that provides us with the experimental procedures to study fear and anxiety.

B. EXPERIMENTAL CONDITIONS FOR THE STUDY OF FEAR

Pavlovian Conditioning

The earliest experiments, and those which have become most important in our understanding of fear, were done by Pavlov (1927). His reasons for conducting these experiments were not to learn about fear and anxiety, but rather to develop the laws for learning about environmental relationships. An important distinction was the one made between the unconditioned response (UR) and the conditioned or conditional response (CR) of the organism. The UR is the direct response that is elicited by the noxious stimulation. Examples put forth by Pavlov include the defensive salivation in response to the sour taste of acid, leg flexion in response to foot shock, and other motor responses to intense physical stimuli such as a pin prick. Pavlov recognized the importance of the psychic (i.e., emotional) component of this direct response to the strong stimulation and, more importantly, the ability of this emotional component to move forward in time and anticipate the occurrence of the painful stimulation. Pavlov studied this phenomenon in considerable detail, but the three paradigms shown in Figure 4-1 demonstrate the most important principles that he developed:

Delay conditioning

The delay conditioning procedure can also utilize long delays with somewhat different results. In this procedure, the CS is gradually presented for longer and longer periods of time until there is eventually a

long delay between the onset of the CS and the occurrence of the painful US. Pavlov found that the animals not only could bridge this gap in time, but ultimately were able to appropriately delay the occurrence of the CR until it just preceded the arrival of the US.

Trace conditioning

The trace conditioning procedure involves a brief presentation of the CS, a period of time during which no stimulus is presented, and then the presentation of the painful stimulus. Under these conditions, the anticipatory responding is slower to develop and more fragile, but the success of the procedure provided the necessary demonstration that the conditioned response could be based upon the memory (trace) of a previous stimulus.

In summary, Pavlov developed the experimental procedures to study the important facts that emotional behaviors such as fear do not require the actual presence of an aversive event, but can be triggered (in a lawful fashion) by events that have reliably predicted the occurrence of aversive events. As we shall see later, it is this separation in time of emotional behavior from the actual events that elicit the original response that forms the basis for the development (and treatment) of stress disorders.

Instrumental Conditioning

Escape learning

Pavlov's experimental procedures involved the physical restraint of the subjects, thereby limiting the types of anticipatory responses that could be made. The experimental procedures that evolved in the United States involve much less restraint and allow more global response patterns to be emitted. One of the more common parallels to Pavlov's unconditioned response places the subject (usually a rat rather than a dog) in a long, narrow alleyway that has an electrified grid floor (see Fig. 4-2). The subject can escape from this painful stimulation by running to the opposite end of the alley and stepping into the non-electrified goal area of the box. Note that the subject's behavior is *instrumental* in escaping from the aversive stimulation. Learning is evidenced by progressively faster running speeds.

Avoidance learning

This simple escape procedure is typically modified to include an initial warning signal (i.e., a CS) that allows a brief period of time to reach the goal area before the shock (US) arrives. Thus, the rat can either avoid the shock by traversing the alley during the presentation of the CS or, failing that, can escape the shock that follows several seconds later. For the philosophically myopic, the ability of the rat to rapidly learn to avoid the impending shock so readily was a problem: Was the rat performing some behavior that was based upon some future set of events? Well, of course it was, but the acceptance of this notion was aided greatly by the proposal of the so-called two factor theory of avoidance behavior.

Two factor theory

Some of the early experimentalists saw the distinction between classical and instrumental conditioning as being too arbitrary, and suggested that instrumental conditioning may include a component of classical conditioning (e.g., Mowrer, 1939). The two factor theory suggests that avoidance behavior is based upon a combination of classical (Pavlovian) conditioning and instrumental conditioning. The subject first learns the environmental *relationships* that exist according to the laws of Pavlovian conditioning, for example, the onset of a light (CS) is reliably followed ten seconds later by the onset of shock (US) to allow the development of anticipatory fear. (Other stimuli such as handling, the characteristics of the testing chamber, etc., can also serve as CSs). Once this anticipatory fear has been established, the organism can learn the environmental *contingencies* that are based on the fact that certain responses are instrumental in terminating either the fear-producing CS or the actual pain-producing US. Thus, the notion of conditioned fear becomes an important determinant in the selection of behavior, and the so-called avoidance responses are actually responses that escape this conditioned fear.

Generalized fears

In the simple experimental procedures described above, the conditioned fear plays a straightforward, even positive, role in guiding the behavior of the organism. There are, however, a variety of situations in which the same fear response interferes with ongoing behavior and, as we will see shortly, contributes to the harmful physiological effects of stress. One of the early demonstrations of a learned fear response that is basically nonproductive was Watson and Rayner's (1920) somewhat infamous experiment with Little Albert. A few presentations of a white stuffed toy (CS) followed by a loud noise (US) resulted in a learned fear response that could be elicited by the presentation of the CS alone. In fact, this learned emotional response was elicited not only by the original stuffed toy, but by other similar white furry objects-- a phenomenon called stimulus generalization. Although the procedures and the underlying processes of learning are essentially identical to Pavlov's simple conditioning procedure, the resulting conditioned response seems less adaptive than leg flexion in a restraining harness. The conditioned fear in these types of situations can be maintained for long periods of time, perhaps indefinitely, through interaction with other behaviors. Individuals who have such fears (e.g., phobias) typically adopt behaviors (avoidance responses) that prevent or minimize contact with the fear eliciting stimuli. This not only results in undesirable restriction of unrelated activities, but also allows many situations that are only remotely related to elicit low levels of fear or anxiety in anticipation of approaches to the original stimulus.

Conditioned emotional response

This interference with unrelated behaviors formed the basis for another experimental model which is termed conditioned emotional response (CER) or conditioned suppression (cf., McAllister & McAllister, 1971). In this procedure, some baseline behavior such as lever pressing for food reward is established. After stable rates of responding have been attained, a long-lasting CS (e.g, a 90-sec tone) is presented and terminates with the presentation of a brief intense shock. After a few such pairings of the tone and shock, the subject will suppress responding during the CS presentation, even though the food reward

contingency is still in effect, and completely independent of the tone-shock pairings. The usual interpretation of this is that the tone elicits a conditioned fear response which is incompatible with feeding. This procedure has been used in countless experiments as the prototype of situations in which conditioned fear interferes with other, unrelated behaviors. Ironically, the powerful influence of the CER situation can be attributed to the actual *lack* of relationship to the lever pressing that is food rewarded.

Punishment

The punishment procedure contrasts sharply with the noncontingent shock presentation that characterizes the CER. Punishment procedures specifically deliver an aversive stimulus each time a particular response is made, and have the advantage of greatly narrowing the range of suppressed behaviors, leaving most other behaviors unchanged. Another way of looking at this phenomenon is that the behavior per se comes to serve as the CS which predicts shock. Other behaviors do not predict shock and, hence, do not lead to the learned fear that suppresses ongoing activity.

Conflict

Punishment procedures are not without problems. To the extent that the behavior in question is strongly motivated, the delivery of punishment can lead to a situation of conflict. One of the most widely used conflict procedures which will be referred to in several cases later, is the procedure developed by Geller and Seifter (1960). This procedure combines several elements of the experimental situations that have been described above. First, the subjects are trained to press a lever to obtain some positive reinforcer such as food, which is usually presented on a variable interval (VI) schedule of reinforcement. After behavior is well established, a long-lasting CS is presented. Unlike the CER situation, this CS does not signal the actual delivery of a shock, but rather signals the presence of a punishment contingency in which every response is accompanied by both food reward and a brief shock. This situation provides a clear marker for the punishment contingency, and shock levels and food motivation can be varied to maximize or minimize the level of conflict.

Two way avoidance

Finally, it should be noted that conditioned fear can interfere with fear motivated behavior as well as with positively reinforced behaviors. One situation in which this is especially salient is the two-way avoidance situation. In this task, a CS such as a light is presented in one end of an alley, followed by the delivery of foot shock. The subject can escape (or avoid) the shock by shuttling to the other end of the alley. After a period of time, the CS is presented in the other end of the alley, and the subject must return to the original location in order to escape or avoid the shock. Thus, there is no actual safe location, but rather the organism must learn that the CS signals the onset of "local" shock which can only be avoided by returning to yet another location in which shock already has been experienced. Of particular importance in considering this type of behavior is that increases in the amount of fear (i.e., higher shock intensities) actually slows down the rate of learning (cf., Moyer & Korn, 1964). The conflict in this situation interferes with learning to such an extent that typical rats require dozens or hundreds of

responses to learn the task, while many do not learn at all.

The Human Condition

The experimental procedures described above, along with many variations, have been used extensively in basic research related to learning and the aversive control of behavior. Although it is an oversimplification, these tasks bear a reasonably close relationship to the various categories of psychiatrically important fears that may be encountered in the clinic.

The simple conditioning procedure can set the stage for both the normal, benign fears of everyday life and the more debilitating phobias. The distinction lies primarily in the time course and severity of the conditioned fear, as well as the object of the fear. In many cases, the conditioned fear response is only weakly established and transient, owing to the lack of a consistent relationship with a strongly aversive stimulus. Such fears are of little consequence. However, a strongly based fear of a common object or situations (e.g, elevators, bridges, cats, etc.) can be maintained indefinitely and even strengthened over time, owing to the individual's ability to avoid contact with the feared object.

In situations in which the object of the phobia cannot be avoided, the resulting influence on behavior is comparable to that observed in the CER procedure. The fear that results from the presence of the CS interferes with virtually all ongoing behaviors. This lack of behavior is not only debilitating in and of itself, but prevents the occurrence of behaviors that might normally lead to the extinction of the fear.

The clinical etiology of compulsive behavior is considerably more complex, but many cases may have their roots in simple Pavlovian conditioning. The disorder is complicated by the interaction of the learned fear response with overt behavior. Just as the punishment procedure described above is effective because the behavior itself comes to serve as a CS that signals an aversive consequence, behaviors that are a part of the compulsive repertoire can serve both to elicit the fear and then to reduce it, setting up a vicious cycle.

Vague or nonspecific anxieties are perhaps the most common form of debilitating fears. As the terms implies, there is frequently some degree of uncertainty about the actual source of fear. Furthermore, these vague fears can build upon themselves, such that individuals begin to fear that certain situations may lead to fear. In Pavlovian terms, this would be fear that anticipates the arrival of a CS that signals an aversive event. In human terms, it is the "fear of fear itself" that seems to be particularly dangerous.

C. THE BODY'S RESPONSE TO FEAR AND ANXIETY

The Adrenal Flight or Fight Response

The presence of a fear eliciting stimulus, whether it be a Pavlovian CS or an aversive stimulus per se, can produce a remarkable set of changes in the body's physiology. This set of changes is orchestrated

primarily by the autonomic nervous system as outlined by Cannon (1929) many years ago. As a result of the diffuse action of the noradrenergic neurons of the sympathetic nervous system and the outpouring of catecholamines, (epinephrine, norepinephrine, and dopamine) and peptides from the adrenal medulla (see Fig. 4-3) the organism is prepared for intense physical activity. The heart rate and blood pressure are increased to provide more effective circulation of oxygen and energy sources. Blood is shunted away from the viscera to provide more circulation to the large muscle groups, and away from the skin surface to reduce bleeding that might occur as a result of injury. The blood chemistry changes to reduce the clotting time. Glycogen is released from the liver to produce an elevation of blood sugar and the spleen releases additional red blood cells into the general circulation to enhance oxygen carrying capacity. The respiration rate increases as does the effective volume of the lungs. The peptides (cf., Chap. 7 discussion of endorphins) lead to a direct reduction of pain. In general, there is a rapid mobilization of bodily resources to increase both the vigor and the intensity of the organism's response to the aversive situation.

The pattern of reactions described above can be elicited by a wide variety of situations, the major criterion being a situation that offers real or perceived danger. The physiological changes that result have clear, adaptive value by virtue of increasing the likelihood of successfully fleeing or fighting off the aversive situation. Indeed, any local folklore contains at least a few anecdotes of nearly superhuman feats that were accomplished under the influence of the sympathetic stress response.

General Adaptation Syndrome

The beauty of the adrenal stress response lies in the speed with which it prepares the organisms for action, but the resulting changes in physiology simply cannot be maintained for long periods of time. Hans Selye looked beyond this immediate response to stress and made two very important observations: (a) Long term exposure to stressful situations can deplete the organism's ability to maintain the stress response, and (b) The pattern of these deleterious effects is independent of the source of stress. Selye (cf., 1956) outlined a three-stage progression of responses to stress that he termed the General Adaptation Syndrome: Alarm, Resistance and Exhaustion. When a stressor is first encountered, a series of responses is initiated in the autonomic nervous system, the immune system and other defenses to cope with the emotional, behavioral and physiological aspects of the stressor. This is called the Stage of Alarm. The maintenance of this reaction to the stressor, which includes reparative processes such as fever regulation, tissue repair, control of inflammation, etc., is termed the Stage of Resistance. In some cases, the stressor cannot be successfully countered, and the organism enters the Stage of Exhaustion. In this stage, the defenses against the stressor begin to fail, metabolic reserves are depleted, there is a general decline in physiological functions, and serious illness or death ensues.

One of the most important of Selye's observations was that this is a general response that is independent of the situation that initiates it. The three stages of the General Adaptation Syndrome can be triggered by disease, injury, psychological stress, or some combination of these.

Surgical Shock

One of the common sources of trauma that can initiate the stress syndrome is that associated with surgical procedures. Even before the time of Selye, surgeons recognized the dual hazards of their art. Death can result either as a direct effect of surgical complications, or as a result of surgical shock that is not directly attributable to the success of the surgical procedure. The French surgeon, Henri Laborit, became interested in this phenomenon in the 1940's and undertook a program of clinical research and observation that was to have far reaching consequences for the treatment of stress related disorders (cf., Caldwell, 1970).

Laborit recognized that surgical trauma involved intense activation of the autonomic nervous system. Normally, the autonomic nervous system maintains bodily functions within fairly tight limits, automatically adjusting the organism's physiological needs to fit the ongoing requirements. These routine adjustments are primarily the responsibility of the parasympathetic, or vegetative, division of the autonomic nervous system (see Fig. 4-4). But in times of severe stress, these systems can run amok, producing bodily changes that are counterproductive, leading to the life threatening condition that is commonly referred to as shock. Attempts to treat the stress may, in some cases, contribute further to the stress. Laborit stated this with an eloquence that survives translation:

"In fact, perfect lytics are not yet at our disposal and even if one existed, it probably would be effective only in large doses. In that case, an injection of the drug would increase the stress that, when it attains a certain level, elicits organic defense reactions that are quite contrary to our fixed goals (prevention or mitigation of those exaggerated reactions that defend our invariant inner milieu that guarantees liberty but not always life.)

(trans. by Caldwell, 1970, p. 29)

Sudden Death

Laborit was not alone in challenging Cannon's sympathetic model of stress. In a paper that was originally published in 1942, Cannon had suggested that massive overreaction of the adrenal system could lead to Voodoo death (sudden death that was caused by emotional rather than physical stress). The most impressive evidence against this model came from an elegant series of experiments performed by a psychologist, Curt Richter, who investigated this curious phenomenon of sudden death.

Richter's initial experiments bore little or no relationship to the stress syndrome. He had become concerned that the methodical inbreeding of the albino laboratory rat had rendered it too weak to serve as an adequate model subject. He attempted to prove his hypothesis by showing that the albino rat was physically weak when compared to its wild, Norway rat counterpart. He developed an endurance test that involved swimming in a circular tank, equipped with a sort of whirlpool in the center that ensured

continuous swimming. The results of the first experiment were somewhat curious: At optimal water temperatures, most of the rats swam 60-80 hours, but a few died within 5-10 minutes. Why? Richter recalled an earlier observation in which a rat's whiskers (vibrissae) had been trimmed as part of another experiment. The rat began to behave strangely, and *died* about eight hours later! Now, Richter suspected that this might have been related to stress, and clipped the whiskers of 12 rats before doing the swim test. Three of the 12 died within minutes, but the remaining nine swam 40-60 hours. By contrast, *all* wild rats tested in the same way died within minutes and many of them die even without the whisker clipping!

Richter searched beyond the superficial aspects of these results. He suspected that this sudden exhaustion and death of the wild rats might be related to the Voodoo death phenomenon, as suggested by Cannon. The prediction to be made by Cannon's sympathetic model was clear--the release of adrenaline should cause the heart to beat faster and faster until it no longer had time to fill between beats, leading to death in systole (i.e, a contracted heart). The actual results were exactly opposite. The heart rate of the wild rats became slower and slower, with the autopsy showing the heart to be completely engorged with blood. These results bore all the earmarks of a massive parasympathetic response.

Richter tested the notion that this was a parasympathetic response using two pharmacological procedures. In one case, he administered mecholyl (a parasympathetic mimicker) to the albino rats. They quickly acquiesced to the swimming task and sank to the bottom, like the wild rats. In the other case, he administered atropine (a parasympathetic blocker) to the wild rats, which prevented the sudden death in some, but not all of the rats tested. The combination of these results, summarized in figure 4-5 spun an irrefutable conclusion: The sudden death phenomenon was parasympathetic. Why?

Richter pursued the emotional causes of this stress syndrome. Is it possible that the normal, sympathetic response to stress is replaced by a parasympathetic response under extreme conditions? The rats' vibrissae provide a major source of information. Lacking this information in a hostile environment such as the swimming tank, could render the situation hopeless, leading to this paradoxical parasympathetic response. But what about the wild rats? Richter suggested that they may also view the situation as hopeless simply because (being wild) it is more stressful to be handled, and they have never before been in captivity. To test this notion, he allowed several of the wild rats to sink to the bottom of the tank. Then, retrieving them from otherwise certain drowning, he placed them on the table until they recovered, then put them back in the tank. After a few repetitions of this lifeguard routine, the wild rats would swim for many hours. The conclusion, which seems valid, was that the wild rats learned that the situation was not hopeless after all.

The results of Richter's experiments bring up several important points that go beyond the analysis of the stress syndrome:

1. A behavioral phenomenon can be blocked through the pharmacological blockade of the target organ receptor. (Atropine prevented the sudden death in wild rats).

2. A behavioral phenomenon can be mimicked or exaggerated through the pharmacological stimulation of the target organ receptor. (Mecholyl triggered the sudden death in albino rats).

3. Manipulations that change the perception of the environment can either exaggerate a behavioral phenomenon (as in the case of shaving the rats' vibrissae) or block a behavioral phenomenon (as in the case of rescuing the wild rats).

4. The perception of the environment is an important determinant of the nature of autonomic response to stressors.

Ulcers

Executive monkeys

The hallmark of stress disorders is the formation of ulcers. This condition has become synonymous with demanding job situations such as executive positions, and with other situations that involve daily exposure to stressful conditions. The superficial reason for ulcer formation is the release of stomach acids into an empty stomach. The presence of these digestive juices, along with some local vascular changes, lead to the digestion of the stomach lining itself, and can sometimes lead to an actual hole through the stomach wall, a perforated ulcer. The real reasons for ulcer formation, however, can be traced back to the emotional responses that set the stage for this untimely release of digestive juices.

Ulcers are far more than a clinical curiosity. They are painful and even life threatening to the individuals who are afflicted. Furthermore, they account for tremendous financial losses in terms of workdays lost and medical costs. The impact of this disorder has stimulated a great deal of research to determine the cause of the disorder and to develop pharmaceutical treatments for the disorder. Obviously, the best solution would be to eliminate the conditions that initiate the ulcerative process, and toward this end, there has been considerable effort to develop an animal model of the stressful conditions that cause hypersecretion of gastric acids.

The cornerstone of this effort was Brady's (1962) so-called Executive Monkey study. This study is important for historical reasons, even though the basic conclusions drawn from the study were, ultimately, shown to be exactly opposite to current knowledge in the area. Brady trained a group of monkeys to perform a free operant (Sidman) avoidance task which required that a lever be pressed to avoid shock to the tail. If the monkeys allowed too much time to elapse before pressing the lever, an electrical shock was delivered to the tail. The executive monkeys spent each workday sitting in the restraining chair performing this task. The worker monkeys sat in a similar restraining chair with electrodes attached to their tails, but the delivery of electrical shock was entirely dependent upon the executives' decisions. If the executive received a shock, so did the worker. Consistent with the predictions, the executive monkeys eventually developed gastric ulcers and the worker monkeys did not. Unfortunately, these results support the wrong conclusions because of a combination of procedural

details and flaws in experimental procedure. We will return to an analysis of these results later.

The triad design

The most comprehensive behavioral research in this area has been done by Weiss and his associates (e.g., 1968; 1981). These experiments, utilizing rats as subjects, have reached conclusions that are diametrically opposed to those of Brady, but at the same time confirm the actual results of those early studies. Although the testing procedures have varied over the years, most of these experiments have utilized the apparatus and procedures that are shown in Figure 4.6 and outlined below.

The rats were placed into small restraining cages with electrodes attached to their tails. A small wheel, located immediately in front of the rats, could be turned with their front feet. In the prototype situation, there were three testing conditions (a triad) that differed in terms of the degree of interaction each rat had with the shock. Although each of these experiments involved many rats, the testing was always conducted in triads so that the environmental conditions of the rats were interdependent. The experiments will be described separately to demonstrate the major conclusions that were reached by Weiss' research group.

Control of stressors

The most critical set of experiments involved an assessment of the importance of control over the environment. The test triad in these experiments was exposed to the following conditions:

(a) *Escapable*: Electric shock was delivered to the rat's tail at random intervals. Once the shock was begun, it was programmed to continue until the rat turned the wheel with its front paws. Thus, the rat had control over the termination of the shock.

(b) *Inescapable*: This rat's tail was connected to the same shock source as the experimental rat. Although it could turn the wheel, the wheel did not influence the shock. Shock termination only occurred when the experimental animal successfully turned it off. This link to the behavior of another subject is referred to as a yoked control procedure.

(c) *Control*: This rat was maintained in the restraining cage for the duration of the experiment, but was not exposed to the electric shock.

The results of these experiments were clear: The rats in the yoked control condition developed gastric ulcers, the other two groups did not. Contrary to the results of Brady's experiments, the subjects that were in charge of shock decisions were the ones that developed the ulcers. However, if these results are described in slightly different language, they seem to make a lot more sense. The rats that had control (i.e., mastery) over the shock were less stressed than those which were at the mercy of their environment.

Prediction of stressors

A second set of experiments extended Weiss' analysis of the conditions that lead to ulcers. In these experiments the following conditions formed the test triad:

(a) *Signaled*: A signal (CS) was presented at random intervals, followed by a brief, inescapable shock.

(b) *Unsignaled*: Again, the rats in this condition received shocks that were identical to those received by the experimental group. The distinguishing feature was that they did not receive the CS that signaled the impending shock.

(c) *Restrained Only*: These rats received neither the CS nor the shock.

The results of these experiments began to support a more general notion of mastery over the environment. Once again, it was the subjects in the yoked control condition that developed the severe ulcers. The experimental animals received the same shock, but apparently the mere knowledge of when the shock was going to be delivered reduced the stress. They developed very few ulcers.

Presence of Conflict

A third set of conditions begins to come closer to the human conditions that are likely to engender ulcer formation. This is the presence of conflict, which Weiss modeled with the following triad:

(a) *Signaled escape*: A signal (CS) for impending shock was presented at random intervals, as in the experiments investigating the importance of prediction. However, these rats also had control over the shock, in that turning of the wheel could either terminate the shock or, if it occurred during the CS, actually avoid the shock altogether.

(b) *Conflict*: These rats were exposed to conditions that were identical to those of the experimental rats, except that on some trials, the wheel turning response itself was punished with electric shock.

(c) *Restrained Only*: Again, these rats were simply restrained for the duration of the experiment.

The rats in the signaled escape condition of this experiment were completely free from ulcers. As suggested by the separate experiments above, the presence of both prediction and control negates the formation of ulcers. The presence of conflict, however, led to severe ulceration. In some sense, it would appear to be better to have no control or prediction at all, than to have these available but inconsistent. Figure 4-7 summarizes these results.

Stressors Revisited

The results of these experiments support a remarkable conclusion: Noxious stimuli are not inherently stressful. In all of the experiments above, the experimental group received shock that was identical to that of the second group in terms of the interval of presentation, the intensity and the duration. The critical factor was not the presence or absence of electric shock, but rather the presence or absence of what we might call a particular "interpretation" of the electric shock. Prediction, control, and the absence of conflict are the three factors that prevent noxious stimuli from becoming stressors.

Why did Brady get the opposite results? The answer lies within Weiss' experiments. Animals that are exposed to shock (even though it is neither predictable nor controllable) will not develop ulcers unless the frequency of occurrence is fairly high--an occasional brief shock is simply not stressful enough to cause a problem. In Brady's experiments, the executive monkeys were skilled enough to prevent most shock from occurring, so the worker monkeys were not exposed to very many shocks. There are several reasons for the development of ulcers in the executive monkeys. Even though they had control, the free operant situation requires constant vigilance, and there is no external CS to predict the shock. The sessions lasted for hours and the constant requirement of timing responses to avoid shock is obviously stressful. Another important factor was that *all* the monkeys were initially trained in the executive condition, and when about half of the subjects had mastered the task, the remaining subjects were switched to the worker condition. This biased selection of subjects made it even more likely that the executive group would develop ulcers, because later studies with rats have shown (for reasons that are not clear) that rats which learn avoidance responses quickly are also more prone to develop ulcers.

All of this is consistent with the conditions that lead to ulcers in the human environment. The prediction and control of corporate executives is illusory. Although they are required to make decisions, the environment is sufficiently complex that the outcome of the decisions is uncertain and occasionally punished (hence, conflict). It is the menial laborer who has prediction and control by virtue of simple tasks, scheduled daily activities, and known outcomes for most work related behavior. Not that these individuals are immune to ulcers, but the source of the conditions that lead to the ulcers is more likely to be found in the home or social environments of these individuals than in their work places.

The experimental procedures that result in ulcer formation fit into a larger context of situations that produce aberrant responding of the autonomic nervous system. The procedures that produce ulcers do not appear, on the surface, to be life threatening. When compared to the trauma of either a surgical procedure or Richter's swimming task, the lack of prediction or control over electric shock would seem to be rather benign. Yet, the common emotional fabric of all of these is the hopelessness and lack of control of the environment. It is the behavioral *interpretation* of the environment (be it valid or not) that leads to an autonomic imbalance in the direction of parasympathetic over-responding.

D. THE PHARMACOLOGY OF STRESS RESPONSES

The Search for Autonomic Stabilizers

We return now to the Val-de-Grace Hospital in France, where Laborit had been continuing his work on

the pharmacological control of surgical shock. Laborit and other surgeons had already used atropine (another compound that blocks acetylcholine at the target organ) to improve the recovery from surgical shock. This treatment was only marginally effective, so Laborit began using low dosages of curare as a ganglionic blocker. As shown in Figure 4-8, curare has little or no effect on the autonomic target organ receptors, but effectively blocks the nicotinic receptor for acetylcholine that is present in both the sympathetic and parasympathetic ganglia. Thus, curare tended to decrease both the sympathetic and parasympathetic reactivity of the autonomic nervous system. This procedure (sometimes used along with atropine) was somewhat effective, but many patients still went into surgical shock.

One of the effects of surgery (or other tissue damage) is the release of histamine, which is also a potent stimulator of some autonomic target sites. (A common example is the redness of the skin that occurs through local vascular responses when it is scratched.) This response to tissue damage (which Laborit called "silent pain") occurs under anesthesia as well as when an individual is awake, adding to the complications of surgery. By the late 1940's, several antihistamine compounds had been developed, and were being used with some degree of success to control surgical shock. Laborit was searching for what he termed the perfect lytic compound--a drug that would stabilize the autonomic nervous system and, in a sense, "dissolve" the patients' fears. He was somewhat pessimistic, however, because he recognized that a heavy dosage of a drug is itself a stressor that can trigger the stress syndrome (see his quote above).

Despite his pessimism, Laborit saw hope for a lytic compound in one of the antihistamines, namely promethazine. In addition to its effects of stabilizing the peripheral autonomic nervous system, the drug also had mild effects on the central nervous system, resulting in a sort of indifference to the stressful environment. This indifference was in contrast to a troublesome sedative and hypnotic side effect that accompanied many of the other antihistamine compounds. Caldwell (1970) relates an instance in which one of Laborit's patients ran through a red light, even though he was not noticeably drowsy and inattentive. Working with a biochemist in a drug company (Specia), Laborit guided the manipulation of antihistamine molecules to bring about maximal central activity, irrespective of action in the periphery. Finally, on December 11, 1950 the drug that was to launch modern psychopharmacology was synthesized: That drug was chlorpromazine.

The Tranquilizers (

Phenothiazines)

Chlorpromazine was not, perhaps, the perfect lytic that Laborit was seeking, but it was close. When administered to patients prior to surgery, the effect was remarkable. The drug did not cause heavy sedation, thus allowing the patients to remain aware of their environment. They could carry on conversations, answer the physician's questions, and clearly were in contact with their environment. But the drug did cause a certain indifference

to stressful stimuli, greatly reducing the normal preoperative fears, reducing the amount of anesthesia that was necessary to conduct the surgery, and most importantly, reducing dramatically the likelihood of death resulting from surgical shock. Virtually all of these effects are caused through action on the brain rather than the peripheral nervous system. It was an autonomic stabilizer that worked by virtue of changing the perception of the environment. It was, in the words of Laborit, a Pavlovian deconditioner-- stimuli that previously elicited fear were as benign following chlorpromazine administration as they would be if experimental extinction had taken place.

Literally thousands of experiments have been done to test the effectiveness of chlorpromazine, but the acid test in terms of animal experiments would be Richter's swimming test. If the drug is truly effective as an autonomic stabilizer, then it should prevent the sudden, parasympathetic death of rats in the swim test: It did.

The first patient to be treated with chlorpromazine was a young man who had a history of agitated, psychotic behavior. He had entered the Val-de-Grace Hospital in September of 1949 and received 15 shock treatments. In February of 1951, he returned to the hospital and received 24 additional shock treatments (both insulin and electric). In January of 1952, he was given 50 mg of chlorpromazine and immediately became calm. After seven hours, his agitation returned, but subsided again with a second dosage of the drug. Gradually, the drug's effectiveness lasted longer and longer, and the patient was released after 20 days.

It is almost impossible to overestimate the impact of this drug and the related phenothiazines on the care and treatment of psychiatric patients. Prior to the advent of chlorpromazine, psychiatric patients were rarely released from the hospital. The chronic, in-patient population was ballooning, and the care bordered on the barbaric. Straight jackets and restraining chairs were used routinely for the protection of patients and staff alike. Electric and insulin shock treatments were common procedure. There were no alternatives and the patients were more likely to get worse than to get better. Chlorpromazine literally freed the psychiatric patients from their bondage. It effectively reduced their fears and agitation to the point that restraining devices were unnecessary. The drug was not habit forming and tolerance was minimal. Most importantly, the patients were not asleep as they had been with barbiturates and other sedative/hypnotics. They retained their ability to interact with their environment, but were indifferent to the stressors.

With the advent of chlorpromazine, patients went home. As shown in Figure 4-9, their is a dramatic reversal of the in-patient population beginning in 1952. The savings in dollars has been estimated in the billions, and the savings in human suffering is incalculable. The patients were not, to be accurate, cured. But the drug allowed them to regain a sufficiently cogent interaction with their environment to be taken care of safely in a family setting.

The details of the action of the phenothiazines will be presented more fully in Chapter 6, but it is important to consider the development of the drugs at this point because of the impact they had on the investigation of the pharmacology of stress. The immediate success of chlorpromazine made drug therapy in psychiatry a reality, and spawned a major search within the pharmaceutical industry for more, if not better, compounds. As a result, chlorpromazine is simply the prototypical example of a group of chemicals known as phenothiazines, which are sometimes referred to as neuroleptics (in reference to their autonomic stabilizing effects), as major tranquilizers (in reference to the Pavlovian deconditioning effects), and as antipsychotics (encompassing both of the above and the fact that they are especially effective in treating this patient population).

The Antianxiety Drugs (

Benzodiazepines)

The success of chlorpromazine in treating psychotic patients led to an intense search for other drugs that would have a calming influence, particularly on the fears and anxieties that occasionally interfere with the lives of otherwise normal individuals. The phenothiazines were, to some extent, too much of a good thing. The emotional flattening and autonomic side effects were reasonable alternatives to psychotic episodes, but seemed like a high price to pay for the treatment of patients who were, perhaps, a little nervous about their new job. Consequently, the search for new drugs was aimed toward compounds that would calm the day-to-day anxieties while having only minor side effects. The most successful drugs produced by this effort was a class of compounds known as the benzodiazepines, of which chlordiazepoxide (Librium) and diazepam (Valium) are the most commonly prescribed.

These compounds are variously referred to by the name of the chemical class, as minor tranquilizers, and as antianxiety compounds. They are useful and widely prescribed to reduce the tensions and anxieties associated with job and family situations, as well as to relieve or prevent associated problems such as muscle tension and headaches.

The screening of drugs that are potentially useful in treating stress related disorders virtually requires animal models. The financial costs, time requirements, and potential dangers of clinical tests with humans all require that the initial stages of testing be done with animal tests. As a result, there are several testing procedures that are useful in categorizing the drugs and to provide further information about the nature of the behavioral changes produced by the drugs' actions on the brain.

In the discussion above, it was pointed out that one of the major effects of chlorpromazine was something termed Pavlovian deconditioning. The results of animal tests confirm this notion, and it is worthwhile to directly compare the effects the phenothiazines and the benzodiazepines on these types of tests. In appropriate dosages, chlorpromazine (and other phenothiazines) can reduce avoidance responding (i.e., conditioned responses to fear), while leaving escape behavior intact (cf., Cook & Sepinwall, 1976; see Fig. 4-10A).

This selective effect on these two closely related responses provides an excellent initial screen for drugs that are likely to share the antipsychotic effects of chlorpromazine in the clinic. By contrast, the anti-anxiety compounds reduce avoidance behavior only in dosages that are sufficiently large to also impair escape responding (Fig. 4-10B). This nonspecific effect can be obtained by several different classes of drugs (e.g., those that simply impair movement), so this task has little or no utility in screening for new compounds that might serve as anti-anxiety drugs.

There is, however, a task that provides a sensitive screen for potential antianxiety drugs. These drugs seem to be uniquely effective in changing performance in the Geller-Seifter punishment procedure that was described earlier. Initially, this test was used to demonstrate the specific effects of barbiturate drugs, because these were the most widely prescribed drugs for the treatment of anxiety. The specific response to punished responding following barbiturate administration is mirrored by the administration of chlordiazepoxide and other benzodiazepines In this test, the animals that have been treated with the drug show perfectly normal behavior patterns in the food rewarded portion of the schedule, but are markedly different from control animals during the punishment portion. Whereas normal rats will stop responding when the signal for shock plus food is presented, rats that have been treated with one of the anti-anxiety compounds are released from this suppressive effect and continue their high rate of responding.

The Geller-Seifter screening procedure is especially important because it discriminates the anti-anxiety compounds from other classes of drugs. Chlorpromazine and other antipsychotic compounds are ineffective in this procedure. General depressants (e.g., barbiturates) or stimulants (e.g., amphetamine or caffeine) of the central nervous system may alter the punished responding, but only in dosages that have a comparable influence on the food rewarded portion of the schedule.

The Geller-Seifter procedure is not the only method for screening drugs for their antianxiety properties. In fact, this method is so cumbersome and time consuming that its use tends to be limited to those situations that require an especially rigorous test of a drug. Other tests which are, perhaps, not so sensitive are much easier to use. For example, chlordiazepoxide will increase the amount of novel food that a rat will consume (Poschel, 1960; in Sepinwall & Cook, 1978). This is apparently not related to any changes in hunger per se, but rather to the more general response to novel (mildly aversive?) situations. When a rat is exposed to a novel environment, there is an increase in plasma corticoid levels. This index of stress can be effectively blocked with administration of minor tranquilizers (e.g, Lahti & Barshun, 1974).

Finally, a particularly easy method of measuring the response to punishment has been shown with the consumption of salt solutions. Although rats show a positive taste response to a hypertonic solution of sodium chloride, the drinking of this solution is rather quickly limited by the aversive postingestional consequences (the animal becomes thirsty as a result of drinking). The administration of minor tranquilizers will increase the amount of hypertonic salt solution that is consumed (e.g., Falk & Burnidge, 1970).

From Laboratory to Clinic and Back

Receptors for Phenothiazines

The pathway from the biochemist's laboratory to the clinician's administration of a drug is not a one way street. Although some of the screening tests may have face validity, there is always a danger that the aspect of the drug that causes an effect on a screening test is not always the same as the one that causes its clinical effectiveness. This problem can never be eliminated completely, but the level of confidence can be raised when tight relationships emerge on the basis of extensive use of the drug in humans. If a drug or class of drugs has been used extensively in the clinic, it may be possible to make a direct comparison between the clinical results and some laboratory screening procedure. In the case of the tranquilizing drugs, there are two such relationships that are especially instructive.

As shown in Figure 4-11, there is a very strong relationship between the clinical dosage of the various antipsychotic compounds and the ability of these compounds to replace another molecule (haloperidol) from dopamine receptors. The logic is as follows: If the dopamine receptors of a test object are simultaneously exposed to haloperidol and some other compound, the two drugs will compete for the receptor sites. For the sake of illustration, if 100 molecules of a compound that has a strong affinity for the dopamine receptor is pitted against haloperidol, perhaps as many as 80 of these molecules will be successful in occupying dopamine receptor sites. If a weak compound is used against haloperidol, then perhaps only 20 molecules would be successful. In order to get 80 molecules of the weak compound into the receptor sites, a higher dosage (in this example, 400 molecules) would have to be used. (It should be noted that this test is based on the D1 receptor for dopamine; see Chapter 8 for further discussion of D1 and D2 receptors.)

In the clinic, the mechanism of action of the drug may not be known, and efficacy is based upon the relief of symptoms. Drugs that are weaker must be prescribed in larger amounts than drugs that are stronger. When a class of compounds has been given to thousands of patients and dosages have been adjusted, then the compounds can be ranked in terms of their relative strength, or *potency*. Note that this does not necessarily mean that any one drug is better than another, but simply that some drugs are more potent than others (the same relationship would hold if a single drug were "watered down" so that a larger amount would have to be given to achieve an effective dosage). The observation of interest is depicted in figure 4-11 (after Creese et al, 1976). When the phenothiazines are rank ordered in terms of their clinical potency, the list is virtually identical to that obtained when they are rank ordered in terms of their affinity to the dopamine receptor. In other words, the potency of a drug to bind to the dopamine receptor is closely related to the potency of that drug to relieve psychotic symptoms in the clinic. It takes a hard nosed skeptic to believe that this would occur by chance.

In the case of the minor tranquilizers, a comparable relationship can be shown between the clinical potency of these compounds and their effectiveness in blocking the suppression of punished responses in the Geller-Seifter procedure. As schematized in figure 4-12, drugs that must be given in large quantities to produce the desired clinical effect must also be given in large quantities to change the behavior in the

Geller-Seifter procedure.

Receptors for Benzodiazepines

The relationship of the benzodiazepines to neurotransmitter systems remained elusive for many years. These drugs do not significantly alter the brain concentrations of dopamine, norepinephrine or serotonin, although the turnover rate of all of these is reduced. Over the years, the compound known as GABA (pronounced gabbuh; short for gamma amino butyric acid) has gained increasing respect as a neurotransmitter. It is present in virtually every portion of the brain, it has consistently inhibitory effects by virtue of opening chloride channels (cf., Chapter 8), and it is probably the single most plentiful neurotransmitter in the brain (see Olsen, 1987 for discussion). The receptor for GABA has been termed the GABA receptor complex (see Fig. 4-13) and is one of the most interesting developments in neurochemistry. It would appear that there are three interacting receptors on this site: One of them is the primary GABA receptor, which regulates the Cl^- channel. The second is a receptor that responds to sedative and convulsant drugs. The third is receptive to benzodiazepines, and their presence enhances the normal activity of GABA.

There is some possibility that the brain produces endogenous compounds that are comparable to the benzodiazepines. The evidence for these naturally occurring substances is threefold: (a) labeled diazepam is tightly bound to specific receptors, (b) the rank order of clinical potencies of the benzodiazepines is highly correlated with the rank order of the ability of these compounds to displace the labeled diazepine from these receptors (see Fig. 4-14; after Baestrup & Squires, 1978), and (c) exposure to stress appears to block the binding of benzodiazepines, presumably because the sites already have become occupied by some stress induced substance. Furthermore, the rank order of clinical potencies is the same as the rank order of the ability of the compounds to displace this labeled compound from the receptor (cf., Moehler & Okada, 1977; see Fig. 4-15; after Lippa et al, 1978).

Anticholinergics as Anti-punishment Drugs

Drugs that block the effects of acetylcholine on parasympathetic target organs are also extremely effective in blocking the effects of punishment, nonreward, and the debilitating effects of conflict--in animals. Although both scopolamine and atropine have been used in some clinical situations (especially presurgically,) they have not been as useful clinically as the animal data would suggest.

There is a great deal of evidence that the brains systems that are involved with reacting to punishment and nonreward utilize acetylcholine as the neurotransmitter (cf., chapter 2 and Carlton, 1963, for related discussion.) Both atropine and scopolamine (cholinergic blocking agents) alter the behavior of rats in a variety of related situations: Behavior that is punished with shock persists. Behavior that is no longer reinforced persists. Stimuli that signal a temporary period of nonreinforcement (time-out experiments) are ignored. Schedules that require low rates of responding to obtain reward (drl schedules) cannot be mastered. These results have been observed in different laboratories, using different reinforcers and

other testing parameters, and in different species. The conclusion that cholinergic blocking agents reduce the response to punishment and nonreward is almost inescapable.

These compounds have also been used in two other situations that seem even more relevant to the reduction of stress responses. One of these has already been discussed: Atropine injections blocked the sudden death phenomenon in Richter's swimming task. The other involves the two way avoidance procedure. Normal rats have great difficulty learning this task, presumably because a successful avoidance response requires that the rat return to a location in which shock (or a signal for shock) has just been experienced. Scopolamine or atropine dramatically increase the ability to master this task, presumably because it reduces the disabling response to conflict.

When this discussion was begun, it was asserted that these drugs influence the brain systems that control the responses to punishment and nonreward. The evidence for this assertion is strong, but at the same time provides a clue concerning the limited usage of these drugs in the clinic as stress inhibitors. Perhaps the major reason why atropine and scopolamine are not suitable for routine administration in humans is because they are *too* effective in the periphery. Recall that Laborit had used scopolamine as a presurgical treatment prior to the development of chlorpromazine, it was effective in blocking the strong parasympathetic component of surgical shock. Likewise, this type of cholinergic blockade was effective in blocking the sudden death phenomenon in Richter's studies. However, the potency of these compounds in blocking the parasympathetic effector organs is itself a liability. In the case of diminishing surgical shock or preventing voodoo death, certain undesirable side effects can be tolerated. But for routine administration, the accompanying dry mouth, dilated pupils, decreased gastrointestinal activity and other autonomic effects are undesirable.

The progression of drugs that were used in the prevention of surgical shock provides a particularly good lesson of pharmacological principles. Scopolamine and atropine block the effects of acetylcholine at the receptors of the actual target organs (i.e., the smooth muscles and glands) of the parasympathetic system. In other words, the "command system" of the autonomic nervous system may remain functional while the final response is blocked. Laborit went back one step and blocked the action at the autonomic ganglia with low dosages of curare. This resulted in an autonomic stabilizing effect, by reducing activity of both the sympathetic and parasympathetic divisions of the autonomic nervous system. This type of action also had its limitations, because it was, in some sense, masking the final stages of a stress reaction that had already been initiated in the central nervous system. Laborit was seeking a drug effect that would block the initial stress *interpretation* in the brain, and found this effect in chlorpromazine. The major point here is that it is preferable to forestall the stress reaction in its initial stages than to allow it to develop and then block its effect at some later point along its synaptic route.

The problem with scopolamine and atropine is not that they lack central effects, but that they have both central and peripheral blocking activities. In fact, there is strong evidence that the major influence of these compounds on the tasks outlined above is attributable to their effects upon the brain rather than the autonomic effectors. Both of these compounds are amines and in their normal states the nitrogen on the side chain has three radicals attached to it and is neutral. These compounds can be transformed biochemically by adding a fourth radical (methyl) to the nitrogen leaving it with a positive charge. The

resulting compounds (called quaternary amines) are commonly referred to as methyl atropine and methyl scopolamine and have the very useful property of being virtually unable to penetrate the blood brain barrier (cf., Chapter 3.) This property means that nearly all of their blocking effects are restricted to the peripheral parasympathetic effectors, while brain acetylcholine systems are left to function normally (see Figure 4-16).

A typical experimental design compares the behavior of a control group (saline injected) with that of a group injected with standard atropine and that of a group receiving methyl atropine. In virtually every experiment that has been done, the results are clear cut: Standard atropine reduces the response to punishment, nonreward and conflict, whereas methyl atropine (which has the same or even more potent peripheral effects) has no effect on these behaviors. What this means is that the blockade of the parasympathetic organs plays little or no role in the effects of these drugs on stress related behaviors. Virtually all of the effects can be attributed to their action on the brain. In this regard, it would be very interesting to know if methyl atropine would prevent the sudden, parasympathetic death in Richter's swimming task (it probably would not) and if a form of scopolamine that worked only on the brain, but not the periphery, would be a useful drug in the treatment of clinical stress disorders (it probably would). In any event, we are not yet finished with the role of the autonomic nervous system in stress responses, and we soon will see evidence that the peripheral responses are considerably more important than they were once thought to be.

Treatment of Ulcers

As in the more acute instances of shock reactions, the formation of ulcers can be blocked or retarded by the injection of cholinergic blocking drugs such as atropine. It is not, however, the treatment of choice in the clinic for the same reasons as discussed above, namely, side effects. It is one thing to demonstrate the effectiveness of atropine by blocking the formation of ulcers in an animal experiment that lasts a few hours or a few days. It is quite another to use such a broad spectrum drug over a period of years in a human patient.

There are two pharmacological solutions to this problem that reflect importantly different therapeutic strategies. One of these, which we have seen above, is to counter the stress response at the developmental stages in the brain. In this regard, the antianxiety compounds are successful in both experimental models and in the clinic. Chlorpromazine might also be effective, but because of its potency is not routinely used for this purpose. Obviously, another even more desirable (and effective) approach is to eliminate the environmental conditions in the patient's life that lead to the formation of ulcers, but it is not always easy for the therapist to extricate people from their yoked control situations.

The second pharmacological approach is to basically ignore the stressful situation per se and very specifically block the final stage of the stress response at the gastric receptors. As discussed earlier, cholinergic blockade is not sufficiently specific, but there is an alternative. Once again, the roots of this alternative go back to Laborit's work on surgical shock. He referred to the silent pain of the surgeon's knife, recognizing that the tissue damage resulted in a large autonomic response. This was due to the

stimulating properties of histamine (literally meaning amine from the tissues) on autonomic effectors. Recall that Laborit's search for an autonomic stabilizer centered on antihistamines, but most of these compounds had broad actions in both the central and the peripheral nervous systems. Over the years, the research that was spawned by these early problems led to the discovery of at least two types of histamine receptors, called H1 and H2 (see Douglas, 1980, for discussion). Of these, the H1 receptors are far more common, being involved in response to injury, hypersensitivity reactions (allergies), and other conditions. The H2 receptors are far less common, being primarily involved with the regulation of the volume and acidity of gastric secretion (see Figure 4-17). Thus, it is possible to administer an H2 blocking compound that will block the hypersecretion of ulcer producing stomach acids, while leaving most of the remaining activities of histamine unaltered. One of these compounds, cimetidine (trade name, Tagamet), has become one of the most widely prescribed drugs in the world!

E. THE AUTONOMIC RESPONSE: Chicken or Egg?

James-Lange Theory of Emotion

The autonomic nervous system has been linked integrally to emotions since Walter Cannon's classic description of the adrenal response. According to Cannon, and later formulations developed with Bard, the autonomic nervous system served rather like a support system. The organism recognized some emotion provoking stimulus in the environment, analyzed it, experienced the appropriate emotion, and as a result of these processes, triggered the autonomic nervous system into action for the ensuing flight or fight.

William James (1890) proposed an alternative view which, on the surface, seems totally unreasonable. The James-Lange formulation proposed that the emotion provoking stimulus triggered the autonomic nervous system directly (although there was a provision for central nervous system involvement), but the actual *experience* of the emotion lagged behind and depended upon a "reading" of the autonomic reaction. Popular (and overly simplistic) metaphors of this theory proclaim that an individual "...is fearful because he is running from a bear", or "...is angry because she hit somebody." This notion seems to have confused cause and effect.

Cannon (1927) pointed out a series of problems with James' view of the emotional experience: (a) The visceral response is slow to develop. (b) The viscera themselves are rather insensitive, even to physical trauma such as cutting or cauterization. (c) The same response (e.g., an elevated heart rate) can be elicited by fear, running around the block, or falling in love. (d) Patients with spinal injuries that lead to paralysis and loss of bodily sensations experience full emotions. (e) Injections of adrenaline do not result in emotional experiences. At the time of this argument, Cannon was perhaps the ranking physiologist of the world, and William James was merely a gifted writer, philosopher, and psychologist who was treading on the foreign soil of physiology. Cannon's view prevailed.

Cannon's professional stature overshadowed some of the weaknesses of his objections. However, the

weaknesses became more and more apparent as additional information about the autonomic nervous system unfolded through the years. It is true that visceral changes are sluggish and slow to develop, but so is it true that the full emotional experience is often slow to develop. An all-too-frequent experience is the near miss of an automobile accident which almost instantly mobilizes complicated motor responses, while the full range and impact of the emotions may come seconds, minutes, or even hours later. It is also true that the viscera can be cut, cauterized and otherwise insulted during surgery with little or no sensation to the patient, but this is a moot point. We certainly can experience the rapid heartbeat, flushed skin, and butterflies in the stomach during emotional experiences. Cannon's point about the origins of an increased heart rate was also weak, in that he failed to recognize the possibility that different emotions engender different patterns of autonomic responses (cf., Ax, 1953; Ekman, et al, 1983; Funkenstein, 1955). Patients who lack the ability to move or to feel somesthetic stimulation of the body still retain a large portion of autonomic sensitivity via the cranial nerves, especially the vagus nerve. These patients also report a lack of emotional intensity, feeling "as if" they were angry. Finally, the experiments involving the effects of adrenaline injections were incomplete in design, missing an important point that even James missed. These studies form the basis for the remainder of this section.

Schachter and Singer's Model

The experiments of Schachter, Singer and their colleagues (e.g., Schachter, 1971; Schachter & Singer, 1962) have shed new light on the James-Lange theory of emotions. Their results show clearly that autonomic arousal can set the stage for (rather than being the result of) emotional experience, and elucidate some of the difficulties that other experimenters (including Cannon and James) have had in triggering emotional reactions with adrenalin injections. We turn now to a consideration of some of their results.

A typical experimental procedure employed by Schachter and Singer involves the injections of either adrenaline or saline (a placebo) and the presence or absence of an emotion provoking situation. In each study, the subjects who had received the injections were divided into two groups. One group simply filled out a questionnaire that contained some rather pointed items. The second group filled out the same questionnaire, but a confederate who pretended to be a subject vividly expressed his outrage at the nature of the questions, tore up the response sheet, and stomped out of the room. Post-test interviews showed the following pattern of results: (a) The questionnaire per se did not elicit anger for either the subjects injected with the placebo or those injected with adrenalin. (b) The subjects injected with the placebo did not experience anger, even when exposed to the confederate. (c) The subjects who had received adrenalin injections, however, were strongly influenced by the confederate and experienced anger over the nature of the questionnaire.

The interpretation of these results is that the emotional experience requires both autonomic arousal and a relevant cognition about the environment. Extending this notion further, it was proposed that the subjects explained their autonomic arousal by attributing it to the anger about the questionnaire, as expressed by the confederate. Since the questionnaire alone was a rather mild stimulus, it could not provide a sufficient account for the autonomic arousal until the flame was fanned, so to speak, by the

confederate.

The explanation outlined above would be very tenuous, were it not for the complementary results of additional experiments. One such experiment used exactly the same treatments (adrenaline or placebo) and the subjects were asked to fill out a long and tedious questionnaire. This time, the confederate rebelled against the tedium of the task and began a high spirited game of basketball, using the wastebasket and some extra copies of the questionnaire. The pattern of results was the same: There was no particular emotion attached to the questionnaire per se for either the placebo or the adrenaline groups. Likewise, those subjects who had received the placebo paid little attention to the confederate. However, those subjects whose sympathetic nervous systems had been aroused by the adrenaline were strongly influenced by the antics of the confederate as revealed by their post-test expressions of euphoria.

There is a great deal of power in these two experiments. A particular emotion cannot be ascribed to the effects of a drug, the adrenaline. Nor can an emotional experience be triggered by the mere presence of a mild environmental situation. But the combination of sympathetic arousal and an appropriate environmental situation can produce a full blown emotional reaction. In the words of Schachter and Singer, the subjects who have been injected with adrenaline have a state of arousal that is in search of an appropriate cognition. These results have been extended in a number of novel designs, including one in which prior adrenaline injections increased the number of belly laughs during a slapstick comedy film. The framework of this theory has even included a naturalistic setting in which male subjects who had just walked across a high suspension bridge (presumably providing their own adrenaline) rated a female confederate significantly more attractive than males who had not crossed the bridge.

A final experimental manipulation provided the capstone for this notion of emotional experience. If the subjects were informed that the drug that they had received was adrenaline and told that it would produce an increase in heart rate, some flushing of the skin, and a general feeling of arousal, the emotional experience was forestalled: The symptoms were attributed to the drug action rather than to the antics of the confederate or the humor of the comedy.

The results of these experiments add a new dimension to the effects of various drugs, especially those that are designed to stabilize emotions or reduce anxiety. It is clear that the effects of these drugs could be either on the central interpretation of the environment (i.e., the cognition) or on the peripheral arousal aspects. It is very likely that the autonomic stabilizing effects play an important role in changing an individual's interpretation of the environment. Just as the subjects in Schachter's experiment say, in essence, that they must be experiencing an emotion because that is the only explanation they have for their state of arousal, so is it possible that an individual whose autonomic nervous system has been stabilized by an antianxiety agent may conclude that the situation must not be anxiety provoking because there is no autonomic arousal. Figure 4-16 shows a summary of some of these effects.

F. SUMMARY

Principles

1. A variety of different experimental procedures have been developed as models of situations that produce fear or anxiety in the natural environment. These procedures systematically vary the exposure to aversive events, the stimuli that signal these events, and the role of behavior in changing these relationships.

2. Pavlovian conditioning procedures show that fear can be evoked by previously neutral stimuli that have been paired with aversive events.

3. Instrumental conditioning involves two factors: Pavlovian conditioning of fear responses and learning of behaviors that are instrumental in changing these relationships.

4. The major response to short term stressors is the so-called flight or fight response of the sympathetic nervous system.

5. Longer exposures to stressors can result in the progressively more severe stages of the General Adaptation Syndrome.

6. Acute trauma such as surgery can lead to the shock syndrome, a diffuse outpouring of the entire autonomic nervous system.

7. The lack of a coping response for acute, profound stressors can lead to sudden death through overreaction of the parasympathetic nervous system.

8. The response to stress can be systematically changed by behavioral and pharmacological interventions.

9. The major forces that lead to ulcers are the inability to predict or control aversive events, and the presence of conflicting consequences (sometimes rewarded; sometimes punished) of behavior.

10. The stress response is more closely related to the interpretation of the environment than to the physical intensity of the aversive stimuli.

11. The search for better stabilizers of the autonomic nervous system led to the discovery of chlorpromazine and related phenothiazines known, collectively, as tranquilizers or antipsychotic drugs.

12. The benzodiazepines rather specifically reduce the effects of punishment, and are widely prescribed (e.g., Librium and Valium) as antianxiety drugs.

13. The phenothiazines have a high affinity for dopamine receptors.

14. The benzodiazepines have a high affinity for specific receptors that have not been linked to the GABA receptor complex. The presence of these receptors has suggested the possibility of an endogenous antianxiety compound in the brain.

15. Anticholinergic drugs appear to have excellent anti-punishment properties in animal experiments, but because of the peripheral side effects, they have little clinical value in the treatment of day to day anxieties.

16. The quaternary forms of atropine and scopolamine have been useful experimentally because they block cholinergic synapses in the periphery, but do not cross the blood brain barrier.

17. Cimetidine (Tagamet) is a very specific blocker of the H2 histamine receptor, and is widely prescribed to reduce the gastric acid secretion that can lead to ulcers.

18. Feedback from the autonomic nervous system plays an important role in determining whether or not an emotion will be experienced; environmental cues interact with this feedback to determine the nature of the emotional response.

Terms

Alarm reaction

Anticholinergics

Antihistamines

Atropine

Avoidance learning

Benzodiazepines

Blood brain barrier

Catecholamines

CER

Chlorpromazine

Cimetidine

Clinical potency

Conflict

CR

CS

Curare

Delay conditioning

Dopamine

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GABA

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Generalized fears

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Chapter 5

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PAIN AND OTHER STRESSORS

A. INTRODUCTION

There is nothing that rivets the attention of an organism quite like pain. It is the first line of defense against environmental situations that threaten the existence of the individual. Each of the sensory modalities has upper limits at which intense stimuli become painful. Although we can recognize the difference between a painfully bright light and a painfully loud sound, there is a commonality among intense stimuli that transcends the modality, placing loud noises side by side with ingrown toenails, aching teeth, and of course, electric shock.

There are many factors that influence the quality and quantity of pain, the most obvious being the physical intensity of the stimulus that is producing the pain. But other parameters also can have powerful influences on the interpretation of pain. The acute pain produced by hitting a thumb with a hammer may be less bothersome than the milder throbbing of a chronically injured knee. Mowrer (1956) put forth a model of fear which, among other things, postulated that the aversive quality of an intense stimulus

included both pain and fear of more pain. Mowrer's theory was complicated and difficult to support, but it presaged by a couple of decades the important distinction between predictable and unpredictable pain.

The involvement of pain in a wide range of human conditions has led to all sorts of remedies for the reduction of pain. Some of these are behavioral and almost reflexive in nature, such as sucking on a thumb that was hit or grasping a barked shin with the hands. This application of pressure may have some physiological basis for pain reduction because of the stimulation of alternative pathways that may actively compete with the processing of pain information. Along the same lines, we may even bite a knuckle to reduce pain in the foot or, in the frontier tradition, bite a bullet instead of a knuckle. The application of cold or heat is also widely prescribed as a physical means of reducing pain.

The ancient folk remedies also include the pharmacologic reduction of pain, the most notable of which are alcohol and the opiate compounds. As modern pharmacology began the systematic search for drugs, the anesthetic compounds (both local and general) were developed. Interestingly, there was some reluctance to use these compounds, partly because of the unknown actions of these drugs, and partly because of the notion that pain was an important part of the healing response. These objections were soon cast aside, however, and drugs that offer pain relief now comprise a major portion of both the prescription and nonprescription pharmaceutical industry.

The most exciting developments in pain research during recent years have not been in the discovery of drugs, but rather in the emerging story of how the body reacts to pain. As indicated above, pain is essential to allow the organism to minimize exposure to adverse environments. But once this alerting function has been accomplished, there is a diminished need for a continuation of the painful stimulus. (It is not necessary to continue feeling the full impact of the hammer on one's thumb to make one more careful in the future!) Toward these ends, it seems that there are mechanisms for the reduction of continued pain. These findings will form the foundation for the present chapter.

B. THE REGULATION OF PAIN PERCEPTION

Pain Pathways and Measurement of Pain

The distinction between acute pain such as that produced by a pin prick and the more chronic, sometimes throbbing pain that follows is recognized readily on an experiential level. These have been referred to as *1st pain* and *2nd pain*, respectively, and there is evidence that these differing perceptions may have an anatomical basis, with the 1st pain being mediated by larger faster fibers that travel through the lateral spinothalamic tract and 2nd pain being mediated by smaller, slower fibers that pass through the medial spinothalamic tract. Because of this anatomical distinction, it has been possible to reduce chronic pain surgically by the transection of the 2nd pain fibers in the spinal cord or, in some extreme cases, by lesions directed to the thalamic targets of these fibers. In the latter case, some patients have reported that the pain is still present, but they "do not care", suggesting a separation of the emotional aspects from the detection of pain.

The investigation of pain (and its counterpart, pain relief) requires the systematic and quantitative measurement of the phenomena. In humans, this has been approximated by measuring thresholds of reported pain under carefully controlled conditions. These thresholds are not discrete, but can be easily influenced by prior experience, instructions, social expectations, and a variety of other factors. Although this complicates research, it does not necessarily mean that the measure is faulty, but probably reflects the very real changes in the perceptions of pain that are engendered by these conditions.

A number of different procedures have been developed to assess the pain threshold of experimental animals. One of the more interesting of these is the flinch/jump test, which exposes a rat to several series of shocks, in ascending and descending intensities (Evans, 1961). With increasing intensities, for example, there will be a range of low shock levels to which the rat does not respond. Then, as the intensity increases, the rat will begin to show a slight flinch with each brief shock presentation. With further increases in intensity, the rat will actually jump when the shock is presented, the criterion usually being that at least three of the rat's feet leave the grid floor. Once these responses have been determined, the sequence is reversed and descending shock intensities are delivered until the jump response disappears and, with further decreases, the flinch response disappears. This procedure produces reliable threshold determinations for both the flinch response, which is interpreted as the lowest shock level that is detectable as pain, and the jump response, which is interpreted as the lowest level of shock that produces an emotional response to the pain. The test can discriminate, for example, between a drug that locally blocks nerve conduction, and a centrally active analgesic drug that reduces the impact of the pain (see Fig. 5-1). (Some of the readers may have had pain thresholds established by a dentist to determine the relative health of two or more teeth, and will be able to appreciate this difference between simple detection and an emotional response.) Despite the theoretical advantages of the flinch/jump test, this procedure has not been used routinely, because it requires an observer to make a subjective evaluation of whether a particular response is a big flinch or a small jump--not as easy as it might seem. Furthermore, the test is rather tedious and time consuming to administer.

Two simpler tests, both of which use heat as the pain eliciting stimulus, have been used more frequently. One of these is the paw lick test, which involves placing the rat on a specially constructed metal plate which is maintained at a constant temperature. The temperature is set low so that the rat can remain on the plate for several seconds before it becomes painful (something akin to the handle of a skillet, which may seem only warm at first, but nonetheless add a briskness to one's steps when carrying it across the kitchen.) The measure of the pain response is the latency from the time the rat is placed on the plate until it licks its front paw. An even simpler measure is the tail flick response, which can be automated for objective measurement. In this test, the rat (or mouse) is placed in a small restraining cage and its tail is pressed lightly into a groove. A source of heat (usually a light bulb) is directed to the underside of the tail. When the heat reaches the pain threshold, the tail is flicked out of the groove, and the latency between the onset of the heat and the tail flick is automatically recorded. Both of these tests produce reliable measurements of thresholds, and have become the standard tests for determining the analgesic properties of drugs or behavioral treatments (see Fig. 5-2).

We turn now to a discussion of the research that has focused upon analgesia, the relief of pain.

The Discovery of Opiate Receptors

Opium, an extract of the poppy plant, was ensured a place in history many centuries ago through the writings and the art work of early civilizations. Loosely translated, the term narcotic means "numbing" and probably refers both to the direct analgesic properties of this compound and to the more general depressant or sedative properties of the drug in larger dosages. Because of its unique powers and potential for abuse, opium and its derivatives have been the subject of literature, art work, legislation and even wars. Against this backdrop of human drama, a research story has unfolded, the results of which may have more far reaching consequences than all of these other aspects.

The production of opium as a drug was mastered long before there existed any formal knowledge of pharmacology. The harvesting of the poppy pods and the procedures for concentrating and to some extent, purifying the opium has been known for centuries. In the 1500's a Swiss physician, Parcelsus, prepared a relatively pure extract, laudanum, which is still used today. The isolation and chemical identification of the active ingredients did not occur until the 1800's, when morphine (which comprises about 10% of dried opium powder) was isolated and codeine (which comprises less than 1% of opium powder) was identified. Each of these components is an effective analgesic, and each has substantial potential for abuse. Ironically, when analogues of these compounds were synthesized in the laboratory, one of them, heroin, was hailed as the "hero drug" that could relieve pain without causing addiction!

The narcotic drugs produce an excellent blend of direct pain reduction and the attenuation of the psychological trauma associated with pain. These effects are especially desirable for acute and severe pain associated with injuries, most notably those that occur on the battlefield. As information about the various neurotransmitters and their receptor specificity started to unfold (cf., Chapter 2), researchers began to search for the mechanism of action of the narcotic drugs. The basic question was "Which transmitter substance is mimicked, blocked, or otherwise modified by the opioid drugs?"

The answer, curiously enough, was none of the above. Although specific transmitters (e.g., histamine and serotonin) had been linked to pain, the narcotic drugs did not appear to interact directly with these systems. As neuropharmacological techniques became more sophisticated, it became possible to isolate and identify specific receptors through a procedure that measures receptor binding. The procedure (shown in Fig. 5-3) is complicated, but it can be summarized as follows (see also related discussions of receptor binding in chapters 5 and 6): The compound in question is prepared in radioactive form and injected into an experimental animal. At some later time, usually calculated to coincide with known times for maximum action of the drug, the brain is homogenized and treated in various chemical and physical (e.g., centrifugation) ways until a relatively pure sample of the radioactive compound and its attached cellular components has been formed. This substance is, for all practical purposes, the original drug and the brain's receptors for the drug.

One of the problems with the type of experiment outlined above is that a considerable amount of

nonspecific binding can also occur, rendering the results meaningless. Avarim Goldstein's laboratory (cf., Goldstein et al, 1971) had developed procedures that involved special washing of the brain tissue, along with very small amounts of the radioactive drug. Using these procedures and a specific antagonist of opiates, naloxone, Pert and Snyder (1973) were able to show specific binding sites in the brain. Comparison of the relative potencies of various opiate mimickers and blockers showed a close correlation with the ability to bind to these receptors (Fig. 5-4), confirming the notion that these were the receptors that are normally involved in the action of opiate pain relievers (cf., Jaffe & Martin, 1980; Snyder, 1978).

But why should the brain have receptors for an extract of the opium poppy? The only logical answer is that the brain does not have receptors for opium. Rather, the brain must have receptors for compounds produced by the body (endogenous compounds) which happen to share a chemical similarity with the narcotic compounds. Given this conclusion, the race was on to find these chemicals in the body, and to delineate the conditions under which they are released.

In 1975, two groups of investigators (Hughes and Kosterlitz from Scotland and Simantov and Snyder from the United States) independently isolated two substances from pig brain and calf brain that had specific morphine-like properties. Hughes and his associates (1975) dubbed these substances enkephalins, from the Greek meaning "in the head". The substances were small peptides consisting of five amino acids each:

Tyr-Gly-Gly-Phe-Met, and

Tyr-Gly-Gly-Phe-Leu

A decade earlier, Li and associates (1965) had isolated a large pituitary hormone which he called beta-lipotropin (so named because it induces fat metabolism). When the structure of this molecule was shown at a convention, one of Hughes' associates, Howard Morris, was in the audience and made a remarkable observation that can only be likened to recognizing a familiar face in a crowd--he noticed the sequence Try-Gly-Gly-Phe-Met (i.e., met-enkephalin) imbedded in the middle of the long molecule. (See how long it takes you to find it in Figure 7-5 even when you know it is there!) It is suspected that this pituitary hormone may serve as a precursor for at least some of the smaller enkephalins that are formed in the brain.

Later studies have shown that the beta-lipotropin molecule not only contains the met-enkephalin sequence, but several other sequences that are significant to stressful conditions. Positions 4-10 forms the sequence for ACTH, while positions 61-76, 61-77, and 61-91 contain the sequences for alpha-, gamma-, and beta-endorphin, respectively. Because all of these compounds have morphine-like properties, they have been termed endorphins as a contraction for endogenous morphines (Simantov & Snyder, 1976). As indicated in Figure 7-5, the beta-lipotropin is released primarily from the intermediate lobe of the pituitary.

The receptors for these endogenous compounds are located in logically appropriate places. In particular, they tend to be highly concentrated in the limbic system (which is involved with emotional responses), and in the periaqueductal gray area of the brain stem (which is strongly implicated as in pain circuitry).

In summary, there appears to be a system within the brain that can produce opioid compounds and there are specific receptors located in appropriate regions of the brain. We turn now to behavioral experiments that demonstrate the action of these systems.

Pain Reduction Systems

One of the most straightforward schemas of pain reduction systems is that put forth by Watkins and Mayer in 1982. This system, which is summarized in Figure 5-6, involves four types of analgesia: Opioid analgesia from both neural and hormonal sources, and Non-Opioid analgesia from neural and hormonal sources.

The major sources of hormonal opiates arise from the pituitary (especially the intermediate lobe and from the adrenal gland (apparently both the medulla and the cortex of the adrenal). As in the case of other hormones, these opioid compounds are released into the bloodstream and can have their effects on widely dispersed target sites.

There are two major sources of neuronal opiates (i.e., opiates that are released at synapses as neurotransmitters). The arcuate nuclei of the hypothalamus contain a population of cells that are anatomically connected to the limbic system and the periaqueductal gray areas of the brain stem (areas that have been shown to have large numbers of opiate receptors). The second source is an opioid link in the descending periaqueductal gray system. In this case, the opioid transmitter substance inhibits cells that transmit pain signals to the thalamus.

The periaqueductal gray system has a component of fibers that does not utilize an opioid transmitter substance, and there apparently are pain inhibiting compounds (of unknown origin) that are released into the bloodstream as hormones. There is relatively little information about either of these systems, and they are typically discussed in terms of what they are not (i.e., nonopioid) rather than what they are.

The evidence for these four types of analgesia comes from many different experiments, but only a few need be described to show the rationale of these conclusions.

Direct electrical stimulation of the periaqueductal gray system through implanted electrodes produces analgesia. For example, the latency to flick the tail away from a heat source is significantly increased. But what type of analgesia does this represent? The standard test is to determine the response to an opiate antagonist, usually naloxone or naltrexone. If a compound that is known to block the analgesic effects of morphine or opium also blocks the analgesia that is produced by electrical stimulation, then it

seems likely that the stimulation is causing the release of endogenous opiates. Naloxone blocks the analgesia produced by periaqueductal gray stimulation. Further evidence for the opioid nature of this effect comes from drug tests that involve morphine. The analgesia produced by electrical stimulation can be enhanced by the administration of morphine. Furthermore, animals that have been rendered tolerant to the effects of morphine show less analgesia with stimulation, and animals that have become tolerant to the effects of electrical stimulation are less responsive to the effects of morphine. Thus, there are three converging results that support the notion that periaqueductal gray stimulation produces analgesia via the release of endogenous opiates:

(a) Naloxone blocks the effect,

(b) Synergism with morphine, and

(c) Cross tolerance with morphine.

It has also been shown that pain itself is a potent stimulus for the production of analgesia. Watkins and Mayer, for example, have shown that electric shock delivered to the front paws of a rat will produce analgesia, as measured by the tail flick response. The administration of naloxone just before the foot shock will abolish this effect. (Naloxone administered after the foot shock does not diminish the analgesia, suggesting that the effect is triggered by endorphins, but not necessarily sustained by them.) The foot shock induced analgesia also shows cross tolerance to morphine, as would be expected from the discussion above.

These naloxone tests confirm the opioid nature of the response, but do not show whether the opiates are neural or hormonal. This distinction is made on the basis of additional experiments. The removal of the pituitary and/or the adrenal gland (the major sources of hormonal opiates) do not diminish the analgesia. Furthermore, transection of the dorsolateral funiculus (the pathway through which the descending periaqueductal gray fibers pass) abolishes the analgesia. Finally, it has been shown that the direct application of naloxone to spinal neurons in the sacral region (i.e., those serving the tail) will prevent the development of analgesia produced by the shock to the front paws. Thus, all of these data converge to suggest that the front paw shock produces analgesia via the small "opioid link" shown in Figure 5-6.

The next aspect of the story seems rather bizarre at first, but the results have been consistent in the hands of Watkins and Mayer. They have shown repeatedly that rear foot shock also produces analgesia, but the effect is not blocked by naloxone. Removal of the pituitary or adrenal is also ineffective, suggesting a neural rather than a hormonal effect. The fibers involved also appear to travel through the dorsolateral funiculus, but from a different origin within the brainstem. These data imply that the pain reduction is neural, but non-opiate in nature.

Prolonged foot shock and/or immobilization produce analgesia that is blocked by naloxone and significantly reduced by removal of the pituitary or adrenal glands (e.g., Lewis et al, 1982). These data support the notion of hormonal opiates that are released by these endocrine glands into the bloodstream.

Although the details of the system are yet to be described, there is evidence for hormonal systems of analgesia that do not involve opioid compounds. Some types of environmental stressors (e.g, cold water swims) can produce an analgesic effect that is not blocked by naloxone, but which requires the integrity of the pituitary and adrenal glands.

These systems of analgesia are peculiar in that different types of pain and different body locations of pain seem to activate different types of analgesia. But why should the rear feet be connected to a different system than the front feet? And why should brief shocks produce one effect, while prolonged shock produces another? These peculiarities may be more apparent than real: The differing procedures may involve differing levels of shock. An attractively simple model of this has been proposed by Forman and Kelsey (personal communication) in a schema that relates the type of analgesia to the impact of the aversive stimulus (some measure of both the intensity and the duration of the painful stimulus). As shown in Figure 5-7, this model suggests that increasing the impact of the painful stimulus can determine which of the four types of analgesia will be produced, with neural opiate analgesia being the easiest to elicit, and hormonal opiate analgesia being elicited only by prolonged or severe pain. This is consistent with much of the experimental literature, including the forepaw/hindpaw phenomenon if one argues that it is easier for the rat to lift the front paws and reduce the impact of the shock (hence, neural opiate rather than neural non-opiate).

A final observation is that all analgesic effects that are based on conditioning (e.g, a *reminder* of a previous shock can produce analgesia) seem to be based on opiates and can be blocked by naloxone. This appears to be the case even when the original painful stimulus resulted in non-opiate analgesia.

Behavioral Effects on Pain Reduction

Interpretation of pain

The experiments outlined above clearly show that aversive stimulation can produce changes in pain perception. This important influence of the environment on something so fundamental as pain perception came as somewhat of a surprise, but was only the tip of the iceberg in terms of the behavioral interactions that were to be demonstrated. As in the phenomena discussed in the previous chapters, the interpretation of the environment has a profound effect on these systems of analgesia.

The triad design, once again, has been useful in demonstrating the role of behavioral variables in producing analgesia. Although a number of different investigators have used this procedure, a particularly efficient application of the procedure has been developed by Kelsey and his associates (cf., Forman & Kelsey, personal communication). In this procedure, the rats are placed in small restraining cages that have a wheel which can be turned by the front paws. The protruding tail has electrodes attached for delivery of electric shock and can also be positioned in a groove that has a heat lamp for measuring tail-flick latencies in the same session. The typical triad design includes the non-shocked control group, a group that can escape the shock, and a yoked group that receives inescapable shocks. As

might be expected from the results discussed in previous contexts, the rats in the first two conditions show no analgesia, whereas the rats that have no control over the shock show a significant increase in the tail flick latencies (see Fig. 5-8).

It should also be noted that the role of the endogenous opiates goes beyond that of mediating the response to direct, painful stimuli from the external environment. A particularly illuminating experiment has shown the effects of social interactions on these systems (Miczek, Thompson & Shuster, 1982). These investigators allowed mice to establish "residence" in their home cages over a period of time. (This involves marking the territory with odors, etc.) They then introduced another mouse into this home territory. Almost invariably, the "intruder" mouse gets attacked and defeated under these conditions, even if the intruder has a "height and weight" advantage. These interactions involve some actual biting of the intruder, as well as a great deal of species specific social postural signals for dominance (on the part of the resident) and submission (on the part of the intruder). The intruder was placed into the resident cage on 10 trials, and allowed to remain each time until 10 bites had been received. As shown in Fig. 5-9, the exposure to defeat led to increasing amounts of analgesia as measured by tail flick latencies. This analgesia declined within an hour after the last session.

Control experiments showed the specificity of this effect by demonstrating that "intruding" into an empty cage had no effect, even if the mouse was "bitten" by forceps while in the cage. Apparently, the social trauma of defeat is an important aspect of this phenomenon.

This effect was shown to be the result of opiate release by the administration of naltrexone, which blocked the development of analgesia. Furthermore, the opiates appear to be playing a role in the central nervous system rather than peripheral effectors, because the administration of a quaternary form of naltrexone, which does not cross the blood brain barrier, did not block the analgesic effect.

Finally, these investigators showed cross tolerance to morphine. In one case, they exposed the animals to the social defeat for 14 successive days, by which time the tail flick latencies had returned to normal (i. e., the mice appeared to be tolerant to the effects of defeat). After this series of defeats, morphine was also ineffective in changing the tail flick response. Turning the procedure around, they implanted time-release morphine pellets that slowly release the analgesic drug over a period of one week. At this time, the mice were placed into resident cages as intruders. The experience of defeat did not change the tail flick latencies. Thus, the cross-tolerance between morphine administration and exposure to defeat were demonstrated (Fig. 5-10).

Placebo and acupuncture

The endogenous opiates also help to explain two types of pain relief that have long been viewed with suspicion: acupuncture and placebo effects. Mayer et al (1976) have shown that acupuncture does produce a reliable decrease in dental pain, and this decrease is blocked by naloxone. Whether this pain reduction is the result of the neural interconnections proposed by the ancient system of acupuncturists or is simply the result of the patients' belief that it will work, remains somewhat problematic.

Although the Western world was reluctant to accept the validity of acupuncture, a related procedure had been used unwittingly in veterinarian practice for many years. The procedure known as twitching involves the firm squeezing of a horse's upper lip in a rope noose. After a few minutes, the horse appears groggy, and can undergo minor surgical procedures with no evidence of pain. This had been interpreted as distracting the horse's attention from the pain of the surgery, but it has recently been shown to increase endorphin levels and the effect can be blocked by naloxone (Lagerweij et al, 1984). It is also interesting to note that long distance runners can sometimes find relief from painful side aches ("stitches") by pinching the upper lip.

The term placebo means "I will please", and has long been used to designate an inactive compound that is administered as though it is an effective drug. In some cases, this is done quite voluntarily, while in other cases, both patient and physician may be misled. In any event, there is now evidence that the endogenous opiates play a role in at least some of the placebo effects. Dental pain is once again the testing ground. In a second series of experiments, Mayer and associates (1976) found that some, but not all, patients showed a reduction in the pain that they experience after they were given medication that was claimed to be a pain reliever. For those patients who responded with a reduction in pain, naloxone blocked the effect and caused an increase in pain. For those who showed no effect of the placebo, the opiate blocker was without effect (Fig. 5-11). Although a lot of additional work needs to be done, it is probably not the case that placebos work for some people but not others. More likely, placebos probably work for virtually everybody, but the conditions under which they are likely to work may differ from individual to individual.

An Overview of the Pain Response

The evidence is clear that pain bears an uneven relationship to the actual physical intensity of the stimulus. When an aversive stimulus is first presented, it almost always produces an immediate behavioral response, and it may even be accurate to view this as a reflexive response. But the processes that change the perception are triggered almost immediately. The exposure to the painful stimulus triggers feedback mechanisms that dull the intensity of the pain. The ability or lack of ability to control the painful stimulus further modulates this perceptual change. In the next section of this chapter, it will be shown that the experience and interpretation of painful events not only changes the perception of pain, but also has far reaching ramifications in terms of the general ability of the organism to respond to stressful challenges.

C. IMMUNE SYSTEM RESPONSES TO PAIN AND STRESS

Survey of the Immune System

The biological self.

The concept of self has been important in several different contexts. In both philosophy and psychology, the notion of the individual being as a unique entity has been pivotal in writings and theoretical developments. The term is so entrenched in our language, that we rarely notice the philosophical implications when we say, for example, "I'd rather do it myself." Yet, a failure to distinguish the difference between self and others adequately or early enough can lead to profound disturbances that are likely to be labeled psychotic.

If the self really is a unique entity that makes up an individual's being, then it is vital to maintain that entity. This requires two fundamental abilities: The individual must be able to discriminate the boundaries between self and nonself, and must be able to defend against forces that would blur this distinction.

The biological self would appear, at first glance, to be so obvious that the concept would be useless. Physical boundaries alone seem to make the distinction between the self and nonself even plainer than the nose on one's face. The biological self became important when sexual reproduction was "invented" and a unique set of information about one self (or is it one's self?) was merged with the information about another self to create a third self. This new importance of individuality was a benchmark in evolutionary history, but the evolutionary advantages also introduced more stringent requirements to be able to recognize and defend the self against the nonself. The immune system is the first line of defense in this task.

The field of immunology is currently one of the most complicated and most active areas of biological research. The increasing knowledge about this system has all but eliminated several major scourges of mankind, such as measles, smallpox, polio and diphtheria. We can protect our selves by taking the appropriate "shots". The importance of this area to behavioral pharmacology is that the environment and the interpretation of the environment have major effects on the immune system. This has led Ader and others (e.g., Ader, 1981) to coin the term psychoneuroimmunology. We turn now to a cursory treatment of the mechanics of the immune system, to be followed by a discussion of the ways in which behavior can place its mark upon this system to either fortify or break down the defenses of our biological selves.

The normal role of the immune system is to recognize foreign (i.e., nonself) substances and create a locally hostile environment that will eliminate them from the system. This can occur in response to the introduction of disease producing bacteria or viruses, tumor cells, parasites, transplanted organs, inappropriately matched blood transfusions, and a host of other substances. In this, its normal role, the immune system is somewhat of a silent warrior, and does not command the attention of the individual. However, for a sizeable proportion of the population, the immune system becomes very obvious by virtue of its somewhat inappropriate response to substances that pose no real threat to the individual. These are the individuals who suffer from allergies to such things as pollen, cat dander, milk, and jewelry, to name a few. Even more serious than over responding to a harmless foreign substance is a failure to recognize self as self. This can occur in a variety of autoimmune diseases such as arthritis, Parkinson's disease, myasthenia gravis, some forms of diabetes, and others (the list is growing).

There are two major ways in which the immune system can respond to a challenge: One of these is a humoral response which can occur almost immediately in a sensitized individual. This involves substances that were created by the immune system and which circulate in the bloodstream until they come into contact with the specific foreign body. The other is a cellular response that involves the proliferation of special blood cells that can react to the specific foreign substance. This reaction is referred to as the delayed response, because it typically requires about 48 hours to develop. The two categories of immune response are mediated by specialized leukocytes (white blood cells) that arise from nonspecialized stem cells formed in the bone marrow (B-cells) and in the thymus gland (T-cells). Refer to Fig. 5-12 for a schematic diagram of the reactions that are being outlined.

Humoral responses.

The humoral response is initiated when a B-lymphocyte recognizes the presence of a foreign substance, the antigen (refer to Fig. 5-13; after Buisseret, 1982). The magnitude of this response is partially determined by the effects of T-lymphocytes, which are termed helper or suppressor T-cells, depending on their role in the interaction. If this initial encounter is interpreted as a challenge from a foreign body, their is a tremendous increase in the metabolic activity of the B-cell and it begins to manufacture and release antibodies that are chemically specific to the original antigen. These antibodies are the immunoglobulins, of which there are five types and several subtypes. One of these, Immunoglobulin-G, has been strongly linked to populations that are exposed to parasitic worms. This same form appears to be involved in allergic responses, presumably because the suppressor T-cells in some individuals allows the initial reaction between antigen and B-cell to continue.

The immunoglobulins that are released by the B-cells interact with mast cells (so-named because they appeared to the German investigator to be "stuffed"), large cells that are found in connective tissues, in the membranes of the intestines, eyes, and respiratory tract, in the skin, and in the lymph glands. These cells contain numerous granules within their cytoplasm, and their surface membrane has several hundred thousand receptors for antibodies (i.e., immunoglobulins). These receptors are nonspecific, in that they will bind any form of immunoglobulin to the surface of the mast cell. However, when two specific antibodies occupy adjacent receptors, the pair forms a highly specific receptor for the original antigen. This sort of "piggy-back" arrangement is a highly efficient way for a single population of cells, the mast cells, to develop unique sensitivities to any of thousands of potential antigens that might be encountered. (This type of arrangement has not been described for neurons, but it is such a clever mechanism that it would be surprising if it were only used in this one system.) The number of mast cells that have this sensitivity conferred upon them is roughly related to the amount of immunoglobulin formed by the B-cells in their first encounter with the antigen.

Once the mast cells have been sensitized, the system is ready for an immediate response when the original antigen is encountered again. When the receptor pair identifies the antigen, calcium enters the mast cell and the granules move to the periphery and are released in a manner that is comparable to the release of a neurotransmitter substance. These granules are comprised of a group of compounds (histamine, serotonin, heparin, blood platelet activators, etc.), which are collectively termed the

preformed chemical mediators. These chemicals have widespread effects on blood vessels, respiratory membranes, smooth muscles, and the blood itself, producing what is commonly called the hay fever reaction. At the same time, there is also an increase in the production of prostaglandins (which have complicated effects on respiratory membranes, mucous secretions, blood clotting factors, etc.) and the leukotrienes. The leukotrienes are many times more potent than histamine, and are responsible for the asthmatic symptoms of contracted airways, dilated and leaky small blood vessels, and painful, itchy nerve endings. In severe cases of allergy, this set of reactions can lead to what is called anaphylactic shock, including the danger of respiratory collapse and death: Nature's way of telling us that we have encountered a foreign substance.

It should be noted at this point, that virtually all drugs (and foods for that matter) are foreign substances, and might be expected to induce an allergic sensitization. Although some drugs can sensitize an individual and lead to an anaphylactic response (penicillin is one of the most common examples), these reactions are rather uncommon. The reason for this is that the immune system is designed to respond to large, nonself proteins. The sensitization process (i.e., the development of specific receptors) is based upon some small part of the surface of the antigen molecule, which is termed the epitope. The presentation of this epitope alone is usually ineffective. Most drug molecules are small relative to proteins, and even if bound to a protein after administration, the likelihood of sensitization is rather slim.

Cellular responses.

The cellular immune response involves the sensitization and proliferation of T-leukocytes (see Fig. 5-14), which mature in the thymus gland. When an antigen is encountered, it is bound to a special macrophage which presents it to the T-cell. The T-cell receptors represent what has been termed the major histocompatibility complex (MHC), which in some sense, can be viewed as the "self-template" against which potentially nonself substances can be compared. The recognition of a foreign substance triggers the release of interleukin-2 which stimulates cell division in the T-cells and produces a substance called gamma-interferon which stimulates prostaglandin release, causes fever (which also promotes cell division), and stimulates both the MHC receptors and the presenting by macrophages. This positive feedback system causes a marked proliferation of sensitized T-cells that respond to the specific antigen. These sensitized T-cells release a group of compounds called lymphokines that produce a characteristic set of effects: (a) dilation of small blood vessels resulting in local redness and warmth, (b) leaky blood vessel walls resulting in swelling, and (c) congregation of macrophages, including phagocytes for removal of foreign substances, damaged tissues, etc. This proliferation of T-cells and the associated macrophages accounts for the increase in the white blood cell count that characterizes the response to infections and injuries.

The immune system obviously is not a static system. It can respond to any of host of potentially threatening molecules in an efficient and specific manner. However, the likelihood that a particular molecule will trigger a reaction is influenced by both genetic and environmental factors. Buisseret (e.g., 1982) has studied this rather extensively in the case of allergies to milk. The genetic link is strong,

though not complete: If both parents are allergic, the offspring have a 58% chance of being allergic. If one parent has the milk allergy, the offspring has a 38% chance of being allergic. The rate is only about 12% for those who do not have a family history of milk allergies.

Early environmental factors also play an important role. Buisseret (1976) cites an early study by Grulee (1943) which showed that 36% of breast fed babies contracted an infection of some sort and .0.13% died as a result. By contrast, babies that were bottle fed were almost twice as likely to contract an infection (63%) and far more likely to die as a result (7.56%)! This could be attributed, in part, to more sanitary conditions surrounding breast feeding, but the bulk of the effect is probably due to the transfer of immunities via the mother's milk (cf., Appleton & McGregor, 1984). There is also some evidence that breast milk may help to prevent proteins from crossing through the intestinal linings where they can sensitize the immune system. Buisseret (1978) followed up these results with an investigation of the interaction between type of early feeding, genetics, and the likelihood of showing an allergy to milk. As shown in Figure 5-15, the breast fed offspring of parents who do not have milk allergies have virtually no chance of developing the allergy. Bottle fed offspring of parents who have allergies show a 60% likelihood of having the allergy. Clearly, the immune system can be influenced by both genetics and the early environment. Given this degree of flexibility, it should not be too surprising that later behavioral influences can also be demonstrated. We turn now to these effects.

Behavioral Effects on the Immune System

Interpretation of the environment.

When Selye (1956) began his pioneering work in defining stress, he noted that general trauma could result in a decrease in the size of the thymus gland and spleen, as well as a general lymphopenia (decrease in number of leukocytes in blood). Although these and similar effects had been related to the body's lowered ability to respond to an immunological challenge, the degree of flexibility in the immune system and the importance of behavioral factors has only been realized in recent years. For example, one of the more dramatic studies along these lines demonstrated that placing rats on a turntable for a brief period each day dramatically increased the growth of implanted tumors (Sklar and Anisman, 1979). The importance of this finding is that a relatively mild stressor that is not directly related to a specific disease (in this case, the tumor) can greatly diminish the ability of the organism to defend against the disease, once it is encountered.

This early work on resistance to tumors has been sharpened considerably by studies that have looked more closely at the behavioral components. Visintainer and associates (1982) implanted a suspension of tumor cells into the flanks of rats, waited 24 hours, then exposed the rats to a set of electric shocks in the familiar triad design. A control group received no shock, a second group received 60 escapable shocks delivered on a variable interval schedule, and a third group received the same schedule of shocks, but the shocks were inescapable. Only 27% of the rats that received inescapable shocks rejected the tumor, whereas more than half of the control group (54%) and the rats that received escapable shock (63%)

rejected the tumors. The rats in the two shock groups received exactly the same number and duration of electric shocks, but the lack of behavioral control over shock termination doubled the likelihood that the tumor would get out of control and kill the rat!

The ability to reject a tumor presumably requires the ability to launch a cellular immune response. This ability has been assessed more directly in studies that have used T-cell proliferation as the measure of the viability of the immune system. Laudenslager and associates (1983) used the triad design of shock administration during a single 80-minute session. At the end of the session, the took blood from the animals, extracted the leukocytes, and treated the leukocytes with T-cell mitogens (either concanavalin A or phytohemagglutinin, abbreviated CON-A and PHA, respectively). These mitogens stimulate cell division, but the amount of cell proliferation depends upon the tendency of the cells to proliferate before they were removed from the system. These investigators demonstrated that exposure to inescapable shock greatly reduced the amount of T-cell proliferation, whereas the exposure to the same amount of escapable shock had no effect (Fig. 5-16). These results demonstrate two important effects: The lack of a coping response suppresses the immune system's ability to respond, and this suppression is triggered very quickly (recall that the blood samples were taken immediately at the end of the session), even though its effects might not become manifest for days or weeks later (e.g., in the case of a challenge by tumor cells).

Learned immune responses.

There is also evidence that changes in the immune system can be learned. Ader and Cohen

(1982) demonstrated this possibility using a strain of New Zealand mice that are genetically predisposed to suffer from serum lupus erythematosus (SLE), an autoimmune disease. This disease is used as a model for similar disorders in humans, and involves a breakdown of connective tissue and a variety of secondary symptoms such as kidney failure. These mice have a relatively short lifespan which can be prolonged by treatment with cyclophosphamide, a drug that suppresses the immune system. The two groups that were used for comparison were the untreated control group (25% of the mice die of their affliction by the time they are 10 weeks old) and a group that received a standard 8-week regimen of chemotherapy (25% mortality is not reached until about 35 weeks). If the animals receive only 4 injections (during alternate weeks of the 8-week treatment period), the chemotherapy is considerably less effective, and the 25% mortality figure is reached at about 20 weeks. Ader and Cohen used this intermediate level of treatment to test for the possibility of conditioning. Prior to each drug injection, the mice received a distinctively flavored saccharin solution. On the intervening weeks, they received the saccharin solution followed by a placebo injection of saline. The question was, would the immune system be suppressed because of the prior association of the distinctive flavor with the injection of cyclophosphamide? The answer was yes: The rats that received these conditioning trials did not reach the 25% mortality figure until 25 weeks, about five weeks longer than the group that simply received the staggered drug injections.

MacQueen and associates (1989) used a somewhat different Pavlovian conditioning approach to

demonstrate the learned release of preformed mediators from mast cells. In this experiment, they paired an audiovisual cue with the injection of egg albumin (an antigen that promotes mast cell activity) into rats. Later presentation of the audiovisual cue alone stimulated the release of the preformed mediators to the same degree as re-exposure to the antigen itself.

The studies that demonstrate changes in the immune system as a result of learning have important implications for medical treatment. Particularly in the case of chemotherapy for cancer, the drugs such as cyclophosphamide are highly toxic, and conditioning procedures might be able to greatly reduce the amount of drug that needs to be administered. Similarly, a long list of ailments including colitis, irritable bowel, asthma, and various food allergies may have a considerable learned component which can be treated more effectively by behavioral means than by drugs. Another intriguing possibility suggests that learning can confer a degree of immunity against the changes in the immune system. For example, McGrath and Kelsey (personal communication) have preliminary data showing that prior exposure to escapable shock can protect rats from the suppression of immunity that normally results from shock that cannot be escaped.

Interaction with endorphins.

The similarity of the behavioral treatments that suppress the immune system and those that trigger the release of endorphins is probably more than a chance occurrence. Shavit and colleagues (1984) have demonstrated the presence of an opioid link in immunological suppression. In particular, they found that a regimen of foot shock that released opioid compounds also suppressed the number of natural killer cells (rather nonspecific immune cells) from the spleen. Both effects were blockable with naloxone. By contrast, a regimen of foot shock that resulted in nonopioid analgesia had no effect on the immune response and was not blockable by naloxone. Further evidence of this opioid link was suggested by the finding that large dosages of morphine also suppress the immune response.

Implications for receptor function.

These changes in the immune system are particularly important in the area of behavioral pharmacology because of their potential for changing the viability of transmitter systems. This has been most clearly demonstrated in the case of myasthenia gravis. This disorder involves the progressive decline in the function of somatic muscles characterized, as the name implies, by a grave weakening of the muscles. Over the years, some researchers have attributed the disorder to a deficiency of acetylcholine (the neuromuscular transmitter) while others have argued that the disease involves a deficiency in the number or sensitivity of the receptors. Either argument is consistent with the observation that patients benefit from treatment with anticholinesterase compounds.

Myasthenia gravis has been strongly linked to an autoimmune disorder which attacks the receptors for acetylcholine. In 1973, Patrick and Lindstrom extracted nicotinic receptors from electric eels and injected a suspension of these receptors into rabbits. The immune systems of the rabbits recognized the nonself nature of these proteins, and developed antibodies. However, the antibodies were not sufficiently

specific, and reacted not only to the nicotinic receptors of the eel, but also to their own nicotinic receptors. As a result, they developed experimental allergic myasthenia gravis (see Fig. 5-17).

It is one thing to show that myasthenia gravis can be mimicked by manipulation of the immune system, but this does not necessarily mean that this is the normal cause in humans. However, the evidence was soon to follow. Almon and associates (1974) found antireceptor antibodies in 87% of patients suffering from myasthenia gravis. As a result of these antibodies, there was a decline in acetylcholine receptor activity of 70-90 percent. For some reason, these patients have developed antibodies to their own receptor sites. Unfortunately, knowing the cause has not provided the cure. Corticosteroids inhibit the immune response (cf., Fig. 5-14), but such treatment has a host of side effects, many of which are dangerous.

The specific chemical relationships between transmitters, receptor sites, and antibodies provide a generously complicated number of ways in which the immune system can cause behavioral dysfunction. Consider, for example, an experiment by Shechter and associates (1984) which was investigating insulin and insulin receptors, but could be equally relevant to a neurotransmitter system (see Fig. 5-18). They began the series by immunizing mice with insulin from cows or pigs. The mice developed specific antibodies (called idiotypes) to this foreign substance. These idiotypes showed some of the characteristics of insulin, and also triggered the formation of anti-idiotypes which were, in effect, antibodies against the mice's own insulin receptors. As a result, the mice developed symptoms of diabetes.

Autoimmunity and behavioral disorders.

What does all of this mean with respect to behavioral disorders? It is unlikely that we are going to encounter suspensions of eel receptors, and we can probably rest assured that we will not be exposed, for example, to the antibodies that mice have formed against the receptors for one of our own hormones. The point of these experiments is that the machinery is there, and it can easily be tricked into developing immune responses that can interfere with the normal process of receptor activity. Thus, immune disorders (or more specifically, autoimmune disorders) become primary candidates for the cause of not only myasthenia gravis, but perhaps schizophrenia, Parkinson's disease, multiple sclerosis, depression, diabetes, and others. The evidence is already beginning to accumulate for several of these.

An unexpected link between hormones, behavior and autoimmunity has been put forth by Geschwind & Behan (1982). Geschwind formed two groups of subjects who had been identified for extreme handedness. Those in the left handed group showed a 12-fold increase in learning disabilities, but also had a disproportionately high number of artists, musicians, engineers, and mathematicians (skills that have been linked to right hemispheric functions). Curiously, 11% of these individuals had some sort of autoimmune disease, whereas only 4% of the right handers suffered from these disorders. The intriguing link to hormones comes from several different observations. For reasons that are unknown, testosterone inhibits the growth of the left hemisphere and of the thymus gland (a major organ of the immune system). The same region of the chromosome that determines the major histocompatibility complex (the

receptor that determines self vs. nonself) may also influence the weight of the testes, serum testosterone levels, and the sensitivity of the receptors to testosterone.

At the present time, many of these experiments and observations offer little more than hints at possible effects. But the results are tantalizing, and it is very likely that within a few years it will become increasingly clear that the immune system is integrally involved in the causes of many behavioral disorders, the response to drugs, and that behavior can, in turn, modify these interactions.

D. AN OVERVIEW OF THE RESPONSES TO STRESS

An attractively simple view of pain and other aversive events is that they are always bad and that the body always mobilizes its energies to either eliminate the aversive stimulus or to escape from the situation. This simple view is wrong. We have seen in Chapters 4 and 5 that painful stimulus per se are either inconsequential or (perhaps) beneficial. The harmful aspects of aversive stimuli inhere not in the stimuli but in the lack of an appropriate coping response. The ability to predict when an aversive stimulus sill occur is good; the ability to actually control it is better; the ability to predict and control is even better. In the absence of these, the organism can suffer a variety of consequences including ulcers, the release of endorphins, the suppression of the immune system, or even sudden death.

The different responses that occur when the opportunity for coping verses no coping prevails is paralleled by the general anatomical and physiological features of the brain regions that mediate emotional responding (see Figure 5-19). The structures of the limbic system appear to be primarily responsible for analyzing the emotional tenor of our environment. The structures of the limbic system receive information from both the outside world and the body, analyze this information, and contribute to the body's response to the situation via messages to the hypothalamus and pituitary. These structures are involved in many aspects of behavior, but it is instructive, in the present context, to analyze the types of responses that are mediated by the anterior and posterior portions of these two structures.

The posterior regions of the hypothalamus and pituitary are responsible for sympathetic arousal, including the stimulation of the adrenal medulla (to release E, NE, DA, and endorphins) and the adrenal cortex (to release mineral corticoids and stimulate inflammatory responses). There is a tendency to view these responses in a negative light because of the nature of the situations that lead to these responses, but in fact, these are energizing responses that improve the organism's's ability to interact with its environment. Appropriately, these responses occur when the environment affords the opportunity for something effective to be done-- for example, fighting, fleeing, or coping.

The anterior portions are normally involved with a variety of constructive functions: adjustments of the vegetative responses of the parasympathetic system, production and regulation of a variety of hormonal systems, and so forth. But when the organism confronts an aversive situation for which there is no obvious coping response, these anterior regions overreact and produce a physiological environment that causes tissue damage or otherwise disrupts bodily functions. The outflow of the parasympathetic system erodes the ability to mount a physical response, the adrenal gland releases glucocorticoids which, in high

concentrations, can cause tissue damage. The release of endorphins dampens the organism's ability to monitor the environment and may contribute to the suppression of the immune system.

In 1932, Cannon wrote a book entitled *The Wisdom of the Body* in which he repeatedly demonstrated the adaptive and appropriate responses of the body to such things as hunger, thirst, exercise, danger, and so forth. His arguments were and remain convincing-- the accuracy and complexity of the body's responses is nothing less than awe-inspiring. It is difficult, however, to see the wisdom of some of these responses to situations that do not offer prediction or control. One might argue that the body (like the proverbial customer) is always right, and that we do not see the situation with sufficient clarity to recognize the benefits. Alternatively, one might argue that the ability to interact effectively with the environment is so crucial to the survival of complex organism that the system fails to function when these conditions do not prevail. (This latter view will receive further support in the next chapter.)

The diversity of the behavioral and physiological responses has complicated and enriched the ways in which we view drug effects. The phenothiazines, the benzodiazepines, and even the beta adrenergic blockers can each decrease the emotional response, but the mechanisms make more sense when viewed within the appropriate behavioral and neurochemical context. Opium and related compounds are not just blocking pain, they are interacting with a multifaceted system that uses the body's own opiates. The important interactions of the immune system with behavior implies that any drug that changes these types of behavioral responses will also be likely to have indirect effects on the immune system. The next two chapters extend the discussion of these issues through an analysis of two different types of mental illness.

E. SUMMARY

Principles

1. Separate anatomical pathways in the spinal cord carry acute, sharp pain in fast fibers and more chronic, dull pain in slower fibers.

2. Pain thresholds have been determined by several methods, including the flinch/jump test, the paw lick test, and the tail flick test.

3. Opium, an extract of the poppy plant, contains both morphine and codeine; heroin is a synthetic analogue.

4. Specific receptors for opiate drugs have been found in the brain. These receptors mediate the effects of endorphins, a group of endogenous compounds that have morphine-like effects.

5. A large pituitary hormone, B-lipotropin, contains the amino acid sequences for several smaller

peptides that are involved in the stress response.

6. There are four systems of pain reduction: opioid from neural and hormonal sources, and nonopioid from neural and hormonal sources.

7. Exposure to inescapable pain or social defeat results in analgesia. In many cases, depending on the precise environmental conditions, this analgesia can be blocked by opiate blockers and is cross tolerant with morphine.

8. Placebo effects and acupuncture appear to be mediated by endorphins.

9. The immune system is involved with recognizing and defending the biological self.

10. The immune system has two major modes of responding: a humoral response that involves circulating immunoglobulins, and a cellular response that involves the proliferation of T-cells.

11. Relatively mild stressors, if not controllable by the individual, can lead to suppression of the immune system.

12. The failure of the immune system in various ways can increase the vulnerability to diseases, trigger allergies, or lead to autoimmune disorders.

13. Immune suppression can be assessed indirectly y measuring the susceptibility to tumor cells or disease, or it can be measuring directly by determining the amount of T-cell proliferation that results from treating a blood sample with mitogens.

14. Both Parkinson's disease and some forms of diabetes seem to involve an autoimmune response to one's own receptors-- a finding that may have important implications for a variety of behavioral disorders.

15. Testosterone appears to inhibit growth of the left hemisphere and the thymus gland, a finding which may account for the abnormally high incidence of autoimmune disorders in left handed males.

16. The posterior portions of the hypothalamus and pituitary mediate the sympathetic arousal response; the anterior portions mediate the overreaction of the parasympathetic system,the release of endogenous opiates, and other responses that accompany the inability to cope.

Terms

ACTH

Acupuncture

Allergy

Analgesic

Anaphylactic shock

Anesthetic

Antibodies

Antigen

Arcuate nucleus

Autoimmune diseases

B cell

Beta-lipotropin

Bright pain

Cellular response

Codeine

Cross-tolerance

Endorphins

Enkephalins

Flinch/jump test

Heroin

Humoral response

Immunoglobulins

Leukocytes

Limbic system

Lymphokines

Macrophage

Mast cell

MHC

Mitogen

Morphine

Myasthenia gravis

Naloxone

Narcotic

Opium

Paw-lick test

Periaqueductal gray

Pituitary

Placebo

Preformed chemical mediators

Proliferation

Receptor binding

Receptor antibodies

Serotonin

Social defeat

Substance P

T-cell

Tail-flick test

Triad design

DEPRESSION AND THE REWARD SYSTEM

DEPRESSION AND THE REWARD SYSTEM

A. INTRODUCTION

The Nature of the Disorder

Depression at its *worst* is the abandonment of pleasure. Its victims feel a pervasive sadness and futility in their lives. They feel weak, worthless, impotent, and frequently see only one category of behavior that promises a satisfactory outcome--to end their futile existence. They often do.

The depressive mood disorder would be worthy of study even if it were presented only in its clinically important stages. It is not, however, a distinct disease entity that afflicts only a few individuals. As in the case of the anxiety disorders discussed in the previous chapter, depression lies along the normal continuum of behavior, and few individuals will avoid the occasional grasp of depression. Thus, depression is a vital area of study for both its day to day and its clinical manifestations, and as it will become apparent later, a better understanding of the disorder can itself provide some measure of

treatment.

Clues for a Laboratory Model

Pavlovian fear and avoidance behavior

The first real breakthrough that led to our current understanding of the behavioral determinants of depression came as a serendipitous observation in a series of experiments that was being conducted at the University of Pennsylvania. Richard Solomon and his students (e.g., Overmeir and Seligman, 1967; Seligman, Maier and Solomon, 1971; Seligman, 1975) were investigating the two factor theory of avoidance learning that was described in Chapter 4. According to this theory, the avoidance of electric shock in standard experimental situations first involves the learning of a classical (Pavlovian) fear response to the appropriate environmental stimuli, and then the motor responses that are instrumental in reducing that fear (in this case, jumping from one side of the chamber to the other).

Seligman tested this hypothesis by combining the procedures of classical and instrumental conditioning. The experimental dogs were first trained to jump back and forth in the testing chamber. Each excursion reset a timer for a specified period of safety (no shock), while a failure to continue shuttling back and forth resulted in a pulsating foot shock until the subject jumped over the barrier. This free operant avoidance procedure (also termed *Sidman avoidance*) eventually leads to a stable rate of jumping back and forth, with most of the potential shocks being avoided. The assumption of the two factor theory of avoidance is that the relatively constant rate of jumping back and forth is being maintained by the reduction of Pavlovian fear. Presumably a greater fear of impending shock would increase the frequency of jumping, while a lesser fear would decrease it.

Once the subjects had been trained in the shuttle box, they were taken to a different experimental room and placed in a Pavlovian conditioning harness. The dogs were then exposed to traditional Pavlovian conditioning procedures with specific stimuli being paired with the presence or absence of shock to the paw. For example, a tone might precede the delivery of a brief shock (signaling fear), while a buzzer might indicate a period of time that was free from shock (signaling safety).

When the dogs were returned to the shuttle box task, three important observations were made:

(a) The additional Pavlovian training did not change the previously learned response of jumping back and forth over the barrier,

(b) presentation of the Pavlovian shock signal increased the rate of jumping, and

(c) presentation of the Pavlovian safety signal decreased the rate of jumping.

Thus, signals that had acquired the values of fear or safety had the expected results on the instrumental

behavior, even though the buzzer and tone had never been used in the training of the shuttle box avoidance response.

Pavlovian fear and learned helplessness

Although the results of the combination of Pavlovian and instrumental procedures provided support for the two factor theory, these interpretations were rather quickly eclipsed by a second set of findings. As a result of a scheduling problem, it was decided to reverse the sequence of training by first establishing the safety and fear signals through Pavlovian conditioning, and then training the dogs to perform the shuttle box avoidance response. The effects of Pavlovian conditioning were known to be enduring, and there was no reason to expect that the results of this sequence of testing would be any different than that presented above. But different they were: When the dogs that had received Pavlovian training were placed in the shuttle box, they not only failed to learn the avoidance response, but actually failed to jump over the barrier to escape the pulsating foot shock. Their yelping and struggling provided assurances that they were experiencing the shock, but they did not show the normal behavior of jumping over the barrier to the other side. The dogs were fundamentally different than normal subjects.

The onus of this failure to behave was placed squarely on the Pavlovian conditioning procedure. In this procedure, the electrode is actually taped to the dog's paw and both the signal that predicts the shock and the occurrence of the shock are completely under the control of the experimenter. Although the subjects typically struggle during the early trials and perform the well known leg flexion response during the later trials, none of these behaviors has any effect on the occurrence of the shock. The subject, therefore has the opportunity to learn two things: (a) the relationship between the stimulus and the shock, and (b) the fact that its behavior has no effect on the occurrence of shock. When the subject is then placed in a situation in which a behavioral response could change the likelihood of shock occurrence, the previous learning that behavior has no effect on shock prevails, and the dog simply does not respond. In the insightful description of Solomon and his associates, the dogs exhibit learned helplessness.

The learned helplessness effect is not an all or none phenomenon. Not all of the subjects showed the effect, but over 95 percent of the naive subjects learn the shuttling response, whereas only one third of the Pavlovian trained animals learned the response. Furthermore, it should be emphasized that the Pavlovian procedure per se does not render the subjects incapable of instrumental learning. In the first series of experiments, the dogs that had already learned the shuttle box avoidance maintained this behavior without deficit, despite the intervening sessions of Pavlovian conditioning. Presumably, having once learned that a particular behavior can change the likelihood of shock, the subjects show a degree of immunity to the otherwise dramatic effects of Pavlovian conditioning. There are other concessions that must be made. For example, the effect is less pronounced in other species and is not necessarily permanent. However, the basic findings have withstood the ravages of time and the assaults of opposing theoretical interpretations to provide some important insights into the mood disorder of depression.

Contingency space

The learned helplessness phenomenon provides an anchor point for the importance of environmental control, but a more global consideration requires an analysis of what has been termed a contingency space. Suppose, for example, that a subject is in a situation in which a particular response (e.g., pressing a lever) results in a consistent change in the environment (e.g., the termination of shock). This one-to-one correspondence is easily learned by the organism. It is possible (indeed, common) to alter the situation such that not every response is effective in changing the environment. These partial reinforcement schedules do not have a detrimental effect on behavior. In fact, they usually tend to energize the behavior.

There is, however, another side to the environment that frequently is overlooked. It is possible to arrange a situation such that a particular change in the environment only occurs if a particular response is NOT made. Both situations provide equal predictability, and both afford the organism the opportunity to learn about and control the environment. However, the middle ground provides a problem: If the situation is arranged such that an environmental change is equally likely to occur whether or not a response is made, there is no predictability, except that the organism can learn that its behavior has no influence on the environment. This is the realm of conditioned helplessness.

Human models

The conditioned helplessness effect was quickly seen as an important model of behavioral depression in humans. The failure to respond to the environment is one of the major symptoms of depression, and the intriguing evidence that this effect is learned captured the imagination of researchers in the area. The ensuing experiments showed that the conditioned helplessness phenomenon is not simply a laboratory curiosity that is restricted to animals in shock avoidance experiments.

There have been a number of experiments involving human subjects which demonstrate the generality of the response to lack of control of the environment. One of the more instructive series of experiments exposed human subjects to bursts of noise (e.g., Klein & Seligman, 1976). In one of the conditions, the subjects could terminate the noise by pressing a button. The subjects in the other group could not control the noise, but were exposed to the mildly noxious stimulus until it was terminated by the subject in the other condition. When compared to the shock that is experienced in the Pavlovian conditioning procedure, this may seem like a rather trivial manipulation, but the effects were clear. The subjects who had been exposed to noise that they could not control were found to be deficient in a variety of tests. When tested later in situations in which their behavior actually could control the environment, they were less able to recognize the contingencies: They were less successful and less persistent in solving complex problems. They were slower in reaching the solution of an anagram (e.g, unscrambling KCRUT into TRUCK,) and when given a series of these, were less able to recognize a consistent rule (e. g., that PSRIC and RIHAC can be unscrambled into CRISP and CHAIR by rearranging the letters in the same sequence as in the case of changing KCRUT into TRUCK). Thus, a single exposure to a situation in which a lack of control is evident can have demonstrable effects on a variety of cognitive tasks that follow this experience (see Figure 6-1).

The generalization of helplessness from one situation to another has important implications for the clinic. Although nobody would entertain seriously the notion that a few minutes of exposure to uncontrollable noise could produce clinical depression, it is not unreasonable to expect similar occurrences in the normal progression of the disorder. The initial exposure to a situation in which one's behavior is ineffective makes it more likely that other situations will be interpreted in the same way. This interpretation is somewhat self fulfilling, because it reduces the attempts to engage in coping responses. Gradually, these effects can spread, until there results a *pervasive* feeling of helplessness or, if we might coin a term, "*omnimpotence*".

Clues for the Chemical Foundations of Depression

The first demonstration of pharmacological intervention into behavioral depression came (curiously enough) from attempts to treat tuberculosis. In 1951, isoniazid and a derivative called iproniazid were developed for the treatment of tuberculosis. Iproniazid was thought to be especially effective, but the enthusiasm about these results was short-lived when it became apparent that the drug had little or no effect on the actual symptoms of tuberculosis, but rather was elevating the understandably depressed mood of the patients (Delay & Deniker, 1952; Baldessarini, 1980).

With this clue from the tuberculosis patients, it was found that iproniazid (but not isoniazid) inhibited MAO activity. Although iproniazid is no longer the treatment of choice for depressive disorders, these results set the stage for the neurochemical view of the disorder that has been maintained (with considerable modifications) up to the present time.

One of the major pharmacological actions of iproniazid and related compounds is the inhibition of monoamine oxidase (MAO). As outlined in Chapter 2, there are two enzymes that degrade or break down catecholamines. These are MAO and COMT (catecholamine O-methyl transferase). As shown in Figure 6.2, these enzymes are differentially distributed with MAO occurring primarily within the cell, while COMT is distributed in the extracellular space. Neither of these enzymes is a major factor in the inactivation of neurotransmission (see Chapter 2 discussion of reuptake), but probably serve more of a general housekeeping function by preventing the buildup of pharmacologically active compounds from free floating transmitters that escape the synaptic field (in the case of COMT) or from compounds that are not compartmentalized in the cells storage system (in the case of MAO). In any event, the MAO inhibitors seem to produce a gradual enhancement of catecholamine systems, and this effect is correlated with an elevation of mood.

In summary, we have seen that the disorder of depression can be linked to an inability to control the environment, and one of the early treatments of depression suggests a link to the catecholamine systems. The next section will examine these observations in more detail.

B. CATECHOLAMINES AND THE REWARD SYSTEM

Medial Forebrain Bundle and Reward

One of the most exciting findings in the physiological bases of behavior came from Olds and Milner's discovery (1954) that rats would press a lever to deliver electrical shocks to the brain. These results held the promise of better understanding the fundamental properties of reward, and the next couple of decades saw literally hundreds of experiments performed to test one aspect or another of this phenomenon. As the results of these experiments were catalogued, the systematic distribution of the stimulation points within the brain that could sustain lever pressing became apparent. In particular, the points corresponded rather precisely with the fibers and terminals of a large, complex system of fibers called the medial forebrain bundle (MFB), and the anatomical term MFB became virtually synonymous with the functional term, reward system (cf., Stein, 1969).

Pharmacology of Reward

Having established some of the anatomical and behavioral relationships of the reward system, researchers began to focus on the pharmacological characteristics of this system. In general, the results support the notion that the MFB reward system utilizes catecholamines as the neurotransmitter, although there is still some controversy as to the relative importance of dopamine and norepinephrine in mediating the effects of reward.

One line of evidence that supports the role of catecholamines comes from brain stimulation experiments while under the influence of various drugs. One of the more important drugs in this regard is amphetamine, which enhances the activity of norepinephrine and dopamine systems by several different pharmacological actions. In general, amphetamine enhances the lever pressing for electrical brain stimulation. However, amphetamine increases performance in many different behavioral situations, so this effect alone provided only weak support for the notion that the reward system is mediated by catecholamines.

Transmitter depletion

More convincing evidence for catecholamine involvement comes from experiments that interfere with the action of these systems. Reserpine is a compound that has a broad spectrum of pharmacological actions, the most notable of which include the progressive depletion of the transmitters norepinephrine, dopamine, and serotonin. It comes as no surprise that the behavioral results of such depletion are widespread, but one of the behaviors that is lost is the lever pressing for rewarding brain stimulation. The important point is not so much the loss of the behavior, but the return of the behavior. The administration of serotonin precursors have no effect on lever pressing, but the administration of l-DOPA, a precursor of dopamine and norepinephrine, will restore these transmitter substances and restore the lever pressing for brain stimulation and other rewards (see Figure 6-3).

Neurotoxins

The catecholamine link became even more convincing with the discovery of a potent and rather specific neurotoxin called 6-hydroxy dopamine (6-OHDA). As the name implies, this compound is closely related to the chemical structure of dopamine. When injected into an animal, it is readily taken into the cell via the normal mechanism of reuptake. However, once inside the storage vesicles, the drug performs its dastardly deed; it physically destroys the terminals of the neurons, causing a loss of functioning and, in many cases, the death of the affected cells (cf., Thoenen and Tranzer, 1973). Many behaviors remain intact despite this loss of catecholamine containing neurons, but one set of behaviors that does not withstand this loss of neurons is the ability to press a lever to obtain rewarding brain stimulation or conventional rewards such as food or water.

As the neurochemists developed more and more precision in their chemical assays, it became apparent that there was a highly systematic organization of neurotransmitter systems that had their cell bodies in the brainstem regions and projected forward into the forebrain regions, including the neocortex. As shown in Figure 6.4, both dopamine and norepinephrine producing cells contribute to the medial forebrain bundle. It is possible to separately disrupt dopamine or norepinephrine systems by either pharmacological manipulation or discrete anatomical lesions. The results of these experiments are weighing in favor of dopamine, but it seems unlikely that norepinephrine will be ruled out as a major contributor to the operation of the reward system.

Pituitary and adrenal responses

One of the major responses to stress involves the autonomic nervous system (cf., Chapter 4). Acute episodes of stress trigger the release of catecholamines from the adrenal medulla, along with several different hormones (most notably, cortisol) from the adrenal cortex. The release of cortisol is controlled by a pituitary hormone, adrenal corticotrophic hormone (ACTH). The entire pituitary adrenal axis is under complex control that includes emotional responses to stress, negative feedback loops in which cortisol inhibits ACTH release, and circadian rhythms. Of particular interest in the present context, is the observation that cortisol levels normally show a sharp increase upon awakening in the morning. This effect can be suppressed by administering dexamethasone, a synthetic version of cortisol which inhibits the release of ACTH by the pituitary.

Patients who suffer from certain forms of depression (especially melancholia) may show abnormalities in the functioning of this system. In particular, the circulating levels of cortisol may be higher than normal. More importantly, dexamethasone does not suppress the production of cortisol. This so-called dexamethasone suppression test may be useful in diagnosing the type of depression and in verifying the effectiveness of various treatments (e.g., Carroll, Curtis and Mendels, 1976).

Overview

In summary, the evidence shows that the response to reward (either conventional or brain stimulation)

requires the structural and pharmacological integrity of a brain system that has its cell bodies in the brain stem, projects forward via the medial forebrain bundle, and releases dopamine and norepinephrine at its terminals.

But what about the Brain-Behavior-Environment triangle in Figure 6-5? It is one thing to show that interference with this system interferes with behavior, but can it be shown that the presence or absence of reward can influence this system? To answer these questions, we will return to experiments that involve conditioned helplessness.

C. BEHAVIORS THAT CHANGE THE BRAIN'S REWARD SYSTEM

Neurochemical Effects of Helplessness

Isolation experiments

The stress of long-term isolation has been used in several different theoretical contexts(cf., review by McKinney and Moran, 1984). Monkeys reared in isolation show severe deficits in social behavior when they are later allowed to interact with conspecifics, some of which bear a resemblance to human depression (e.g., Harlow and Suomi, 1971). Mice reared in social isolation show equally severe social deficits, including a marked increase in fighting. These isolated mice also showed a decrease in the brain's synthesis and utilization of catecholamines, but these neurochemical deficiencies were reversed by the fighting behavior (e.g., Modigh, 1973; 1974).

The effects of isolation are severe, and certainly go beyond a simple parallel to depression. But the interaction with catecholamines continues the thread of continuity between depression and brain chemistry. Furthermore, these experiments suggest that the self isolation that results in depressed patients may exacerbate the underlying neurochemical causes of the disorder--a point that we shall return to later.

Coping responses

Weiss and his associates (Weiss, Goodman, Losito, Corrigan, Charry, & Bailey, 1981) have investigated the helplessness phenomenon using a combination of techniques that were developed for the investigation of stress reactions (cf., Chapter 4). As in the case of some of the experiments investigating gastric ulcer formation, Weiss and his colleagues have conducted many different experiments, but a common theme is present in all the designs. A typical experiment involved three groups of rats that were tested in the following triad design:

(a) *No Shock*: These rats had electrodes taped to their tails, but did not receive electric shock.

(b) *Avoidance-Escape*: These rats were exposed to signalled tail shock that could be avoided or escaped by pressing a lever.

(c) *Yoked Control*: These subjects received shocks that were identical to those that were received by the avoidance-escape subjects, but they had no control over its occurrence.

The rationale was that the rats in the yoked control condition would learn that their behavior was ineffective and become less likely to exhibit appropriate coping responses in other situations.

The second phase of the study was modeled after Richter's swimming test, but rather than bombarding the rats with a seemingly impossible task, Weiss and his associates outfitted the rats with a flotation device that served as a sort of life jacket. The rats were placed in the swimming tank for 15 minutes, during which time they could either swim around or float passively. As predicted, the rats that had been in the yoked condition spent more time floating passively, while those from the other two groups spent a great deal of time swimming, struggling, and (apparently) attempting to escape from the situation (Fig. 6-6).

Sometimes, a tidbit of data emerges that makes the major results of an experiment even more salient. All of the rats in these experiments had electrodes fastened to their tails with a band of adhesive tape. When the shock session was over, the electrode leads were simply snipped off, rather than further traumatizing the rats by attempting to remove several layers of tape from their tails. Over the course of the experiment, nearly half of the rats in the avoidance-escape group and the no shock group removed the tape from their tails. By contrast, none of the rats that had experienced a lack of control removed the tape!

Enzyme changes

Weiss' experiments continued into the sphere of neurochemistry, and provided some interesting correlations with the temporary nature of the helplessness effect that was observed in Solomon's initial experiments. When norepinephrine levels were measured in the locus coeruleus and anterior cortex (the source and termination of the fiber system), significant decreases in the transmitter were observed, and these decreases were transient in nature (see Figure 6-7).

Further tests revealed that this decline is the result of a reduction of tyrosine hydroxylase, the rate limiting enzyme in the chain of synthesis of norepinephrine. Although the details have not yet been worked out, the transient effect outlined above probably can be made more permanent through repeated exposure to a lack of control. Furthermore, repeated exposure to controllable stress (sometimes referred to as positive stress or eustress) seems to increase the level of tyrosine hydroxylase. Thus, behavioral manipulations appear to have a profound influence on the integrity of the neuropharmacological systems of reward, a matter which will be dealt with more fully at the end of this chapter.

Autoreceptor model

Weiss sees these results as part of a more general pattern of neuromodulation. It appears that there are special alpha-2 "autoreceptors" in the cells of the locus coeruleus that respond to the short collaterals of neighboring cells (see Figure 6-8). These norepinephrine containing cells are mutually inhibitory and, in a sense, provide mutual control over the production of neurotransmitter substance to be released in the anterior cortex. This is especially interesting because we see, for the first time, the dynamic nature of neurochemical systems. The MFB is not simply a brain system that is used under some conditions and not under others. Behavioral interactions with the environment can alter the vitality of this system just as surely as exercise can alter a muscle. Behavior, environment, and transmitter systems are inextricable bound together and effective therapeutic schemes should take this into account.

D. THERAPEUTIC APPROACHES

Special Problems of Treatment

Remission problems

Both the treatment of depression and the evaluation of the treatment have provided a depressing array of problems for clinicians and theorists alike. The depressive mood disorder is rarely a constant symptom. The depressed states typically are recurrent in nature, with periods of spontaneous remission that range from a simple abatement of the depression, to normal moods, to frank manic behavior in the bipolar form of the disorder. It is clearly a moving target, and attempts to treat and evaluate the disorder necessarily encounter a great many false positives and false negatives.

Drug problems

The inherent difficulties of treating a recurrent and remissive set of symptoms are compounded by the nature of the drugs that have been shown to be effective in treating the disorder. The two major classes of drugs that have been used, the MAO inhibitors and the tricyclic compounds, seems to be effective only after several weeks of administration. During this time period, it is possible that the depressive disorder could go into remission or become more severe, irrespective of the effects of the drug. To make matters worse, it seems that the choice of drug and dosage is not at all arbitrary; some patients respond to one drug but not others, and the effective dosage may also be idiosyncratic. When translated into the real clinical situation, the search for a successful regimen of therapy may require many months.

An additional problem is that the antidepressant drugs are dangerous. Both the tricyclic compounds and the MAO inhibitors have strong autonomic and cardiovascular effects, increasing the risk of cardiac failure. This is especially the case with MAO inhibitors, which greatly potentiate the effects of adrenergic drugs, and even amines that occur in foods such as cheeses and some wines. The final irony

is that the antidepressant drugs do not enjoy a high therapeutic ratio. Unlike the antianxiety and antipsychotic drugs which can be withstood in heroic dosages, a few dosages of the antidepressant drugs can be lethal--and this is the population of patients that tends to be suicidal.

The mood of depressed patients seems resistant to the effects of drugs that elevate the mood in normal individuals. Two of the most potent drugs in this category are amphetamine and cocaine. Both of these drugs can produce a rapid and potent elevation of mood in normal individuals, with the resulting effects frequently being described as euphoria. In addition to the direction of mood changes produced by these drugs, they also come with good biochemical credentials for the treatment of depression. The evidence is strong that both of these drugs act through facilitation of catecholamine systems. Figure 6-9 summarizes the effects of these two drugs. Despite the evidence cited above for a model of depression that involves a catecholamine dysfunction, the drugs do not work. Neither cocaine nor amphetamine show any useful degree of clinical efficacy for the treatment of depression.

The Role of Monoamine Oxidase

MAO inhibitors

The enzyme monoamine oxidase normally destroys at least some of the amines that are present in the intracellular fluid of the noradrenergic cells, while transmitter substance that is located within the terminal vesicles or other binding sites is relatively protected from the effects of the enzyme. It has been suggested that the major purpose of MAO is to provide a sort of quality control by destroying the free-floating amines that may have been transformed into compounds that would have undesirable effects if allowed to enter the vesicles and be released as false transmitters.

Reserpine model

Additional insights into the action of MAO have come from studies in which MAO inhibitors are given in combination with other drugs. In particular, reserpine and the related synthetic tranquilizer tetrabenazine act to deplete the stores of catecholamines (NE and DA) and serotonin (5-HT). As shown in Figure 6.10, the primary effect of reserpine is to inhibit (in this example) the storage of norepinephrine in the vesicles. There is, therefore, a reduction in the amount of newly synthesized NE that enters the functional pool, as well as a reduction in the efficiency of recycling the released NE through the reuptake mechanism. The impaired entry of the NE into the protected environs of the synaptic vesicles allows much of the NE to be converted into inactive products by MAO. The administration of a MAO inhibitor along with reserpine allows the accumulating NE greater access to the storage vesicles, as well as allowing some of the NE to be transformed into related compounds (both biologically active and inactive) that may serve as false transmitters.

The interaction of reserpine and the MAO inhibitors has served as a model, albeit not a very convincing one, of the development and treatment of behavioral depression. As noted earlier, reserpine results in the gradual release and depletion of transmitter substance from the neuron. When administered to humans,

this effect is paralleled by the development of severe depression, a so-called side effect.

In experimental animals, there is a comparable decline in behavior, especially under conditions in which behavioral activity is maintained by delivery of discrete reinforcement. Animals that have been trained to press a lever to obtain water, food, or electrical brain stimulation will stop responding as the level of catecholamines decline following reserpine administration. Animals that have stopped lever pressing for reward show a prompt renewal of the behavior when a MAO inhibitor is administered (much like that following l-DOPA administration shown previously in Figure 6-3 above). In fact, the effect is almost too good to be true. The theoretical difficulty of this phenomenon is that the MAO inhibitors produce a rapid and transient reversal of the behavior that was lost through reserpine treatment, whereas the effects of these compounds in the clinic are characterized by a slow onset and more chronic duration of action.

MAO isozymes

Even though the reserpine model falls short of matching the clinical symptoms of depression, the consistent linking of depressive disorders with catecholamines has helped to maintain an interest in the study of MAO inhibitors. As a result, there is now evidence that certain drugs produce a selective inhibition of MAO. There appear to be at least two isozymes (closely related enzymes) of MAO which have different sites of action. Although the distributions overlap, there is a preponderance of MAO-A in the periphery, especially in the liver and intestines. The administration of a specific inhibitor of MAO-B has a preferential effect on the brain amines, and leaves a sufficient amount of MAO activity in the gut and liver to avoid the wine and cheese complications noted above. (Figure 6.11 shows the differential distribution and tyramine role in hypertension through NE release etc.)

Tricyclic Antidepressants

The tricyclic antidepressant compounds have a history that parallels that of the antipsychotic drugs discussed previously in Chapter 4. This history can be traced back to the early search for better antihistamine compounds that led to the development of chlorpromazine and related phenothiazines. The tricyclic antihistamines are, in some sense, the compounds that failed the phenothiazine test. Rather than suppressing the agitated mood of patients, it was observed that some of these compounds elevated the mood of depressed patients.

The major effect of the tricyclic compounds on adrenergic neurons is to block the reuptake mechanism (see Figure 6-12), but as in the case of the MAO inhibitors, the evidence that this forms the basis of the antidepressant effect is less than conclusive. The blockade of the reuptake pathway avoids the dangerous effects of tyramine ingestion via food intake, but leaves the patient vulnerable to a host of other drug interactions. In general, the patients must avoid a wide range of drugs that influence either adrenergic or cholinergic transmitter systems because of potentially life threatening cardiovascular and central nervous system effects.

Whatever the mechanism that accounts for the antidepressant effects, the tricyclic compounds are like the MAO inhibitors in that they typically require two to three weeks to become clinically effective. Furthermore, the elevation of mood seems to have depression as a prerequisite, because the drugs are ineffective in normal subjects. In fact, normal subjects are likely to experience general feelings of discomfort and anxiety rather than an elevation of mood.

Choosing The Drug

One of the major difficulties facing the clinician who is treating depression is the selection of the best drug. Clearly, a part of the decision can be based upon the general health picture that is presented, and some drugs may be contraindicated because of potential interactions with the patient's ongoing medical treatment (e.g., drugs) or with dietary habits (e.g., wine and cheese). There still remains the problem that some drugs may be more effective than others, and it will take a few weeks to find out. Several investigators (cf., Schildkraut, Orsulak, Schatzberg & Rosenbaum, 1984; Leckman & Maas, 1984) have attempted to find biochemical markers that will provide a clue for drug selection. Not surprisingly, this search has centered around the metabolites of catecholamine neurotransmitters.

As indicated in Figure 6-13, there are several alternative pathways for the normal degradation of catecholamines that are not bound in storage sites or synaptic vesicles. There is some evidence that patients exhibiting different symptoms of depression show different levels of particular metabolites. One clue came from patients who were being treated for amphetamine overdose. These patients showed very high levels of MHPG while the drug was running its course, followed by very low levels for two to three days afterward. These low levels of MHPG were accompanied by marked depression. Patients suffering from unipolar depression show a wide range of MHPG levels. Those with low levels tend to respond favorably to tricyclic compounds, or even to amphetamines. Those with high levels respond more favorably to the MAO inhibitors. Another type of marker serves more to indicate the success of therapy rather than predicting the success of the particular drug. Robinson (see Maugh, 1984) has found that another metabolite (DHPG) is low in depressed patients, but consistently increases before the mood level increases. In each of these cases, there is some degree of controversy; some groups of investigators corroborate the results, while others fail. There are, however, sufficient clues to make this a potentially fruitful approach for the selection of therapy.

The model of depression presented here has been deliberately biased toward the catecholamine systems, in part because of the historical emphasis on this system, and in part because it coincides more clearly with the behavioral models that are currently available. It is clear, however, that any comprehensive model of depression must also consider the serotonergic systems of the brain. The major drugs that alter mood levels frequently influence both the catecholamines and serotonin. Reserpine, as indicated earlier, depletes both norepinephrine and serotonin and causes severe depression. The tricyclic antidepressants block the reuptake of both norepinephrine and serotonin, and relieve depression. Some of the newer forms of antidepressants seem to specifically block serotonin reuptake and, as you might guess by now, there are some effective antidepressants that have not been shown to influence *either* system.

These superficial inconsistencies do not necessarily mean that the catecholamine model is wrong. Rather, they suggest that we need a neurochemical model that matches the complexity of the disorder as seen in the clinic. Although there is a commonality of symptoms among patients who suffer from depression, it may be possible (and necessary) to analyze these symptoms and various biochemical markers in some detail before selecting the treatment. One of the metabolites of serotonin, 5-HIAA (5-hydroxy indole acetic acid), has been correlated with suicide attempts of depressed patients (e.g., Traeksman et al, 1981). In a population of patients who are all suffering from depression, those with the lowest levels of 5-HIAA in their cerebrospinal fluid (i.e., lowest utilization of serotonin) are the most likely to attempt suicide-- especially by violent means. On the other hand, the results shown in Figure 6-3 suggest that norepinephrine is more important for the recovery of a normal response to rewards. It seems possible, that the lack of responsiveness to reward and, perhaps, the decline in activity levels may be attributable to dysfunction of the catecholamine systems. The preoccupation with thoughts of death, the attempts to commit suicide, and disorders of sleep may be attributable to dysfunction of serotonergic systems. If this type of dissociation is valid, then a detailed appraisal of behavioral attributes and blood/csf chemistry may greatly increase the likelihood of prescribing an effective drug on the first attempt.

Why the Delay?

Some of the peculiar features of the MAO inhibitors and the tricyclic antidepressants suggest that their effects may not be understood by a straightforward description of their interaction with synapses. Several observations are at odds with an explanation that is based simply on their *immediate* interference with monoamine oxidase or with the reuptake mechanism:

(a) The antidepressant drugs are more effective than either cocaine or amphetamine, both of which produce more immediate and more potent stimulation of the catecholamine systems.

(b) The antidepressant drugs, especially the tricyclic compounds, are ineffective in elevating the mood of normal (i.e., non-depressed) subjects, and seem to have rather selective effects on different forms of depression.

(c) Although both classes of compounds produce a variety of neurochemical effects and are eliminated from the body within hours (or certainly within days), effective therapeutic regimens frequently require as much as several weeks before the abatement of clinical symptoms becomes apparent.

It seems likely that such a delayed onset of effectiveness reflects some long term, tonic change in the neuronal substrate that is being affected. One likely candidate for such a change is a general increase in the storage and release of the transmitter substance (see Chapter 3 for a discussion of functional pools). As mentioned above, Weiss and associates suggest that helplessness may involve a change in the activity of the alpha-2 autoreceptors in the region of the locus coeruleus. The antidepressant compounds may act upon this and other neuromodulatory systems to allow the transmitter system to develop (slowly) the cellular mechanisms that bring it back normal levels of responsiveness. This process might be triggered by a short term action such as the inhibition of MAO or the blockade of the reuptake

mechanism, but not be manifested until the long term changes in the neuron's metabolic machinery have been accomplished. In this particular case, a change in the autoreceptor activity at the cells of origin in the locus coeruleus could alter the level of norepinephrine that is released in more anterior regions of the brain. This effect, in turn, could change the number and sensitivity of the postsynaptic receptors that are involved in regulating the organism's behavioral interaction with the environment (see Figure 6.14). This idea of long term modulation of the catecholamine neurons is also consistent with Anisman's (1984) suggestion that stressors can lead to reduced sensitivity of receptors to catecholamines. All of these effects may be reversible by drugs, but the requirement of metabolic and structural change in the neurons could easily account for the observed delay in the therapeutic effects of the drugs.

Electroconvulsive Therapy

The long therapeutic delay that characterizes the antidepressant drugs is more than an inconvenience. In cases of severe depression, the threat of suicide is so real that more heroic approaches to therapy are sometimes necessary. One such approach is electroconvulsive therapy (ECT), more colloquially referred to as shock treatment.

Electroconvulsive therapy was introduced by an Italian physician named Cerletti (e.g., Cerletti and Bini, 1938) A vagrant, wandering in apparent confusion through the local train station, had been arrested by the police and presented for psychiatric treatment. Cerletti had noted the calming effects of electric shock on animals that were stunned by electricity at the slaughterhouse, and had tried the procedure experimentally on a few dogs. He decided to try the procedure on the newly presented patient, whose identity was unknown. Cerletti concluded that the treatment must have been beneficial, because when the patient was brought in for the second treatment, the previously noncommunicative man exclaimed something to the effect of "My God, No! It's deadly!" It was on this somewhat shaky foundation that ECT began to be used for a variety of psychiatric treatments and as an experimental tool in animal research.

The convulsions that accompanied the early methods of ECT were traumatic. The uncontrolled muscular activity was so powerful that it damaged tendons, dislocated joints, or even broke bones unless the patients were pre-treated with muscle relaxants. The convulsions were followed by obvious (though short term and transient) losses of memory in both humans and experimental animals. There was histological evidence that some neurons died as a result of the procedure. Given the serious nature of the ECT treatment, there could have been only one legitimate reason for using the procedure--it worked.

Modern versions of ECT bear little resemblance to the early methods. The electrical currents are much lower, are restricted to smaller portions of the brain, and are given following pretreatment with anesthesia and muscle relaxants. Unlike the slow acting drug therapies, electroconvulsive therapy can produce a prompt reversal of the symptoms of severe depression, allowing the patient to return to family and job situations much more quickly. More importantly, the rapid effects greatly diminish the risk of suicide that might occur before other forms of therapy would have a chance to become effective.

Experimental studies of ECT in animals provides further support for the role of catecholamines in depression. Neurochemical assays have revealed that ECT stimulates the synthesis of norepinephrine by increasing the level of tyrosine hydroxylase (Masserano, Takimoto and Weiner, 1981).

Clearly, the dangers inherent in ECT should not be minimized, and this form of treatment should not be administered casually. However, it will continue to be used as long as there is no alternative treatment that is as fast and as effective in reversing the symptoms of severe depression.

Lithium Therapy

Lithium is a simple salt that has had a stormy history as a drug. Because of its similarity to sodium, it was used initially as a substitute for table salt in the diet of cardiac patients. Many of these patients died, because the lithium readily replaces sodium in the body but it does not support cellular functions in the same manner as sodium. The use of lithium as a treatment in psychiatric disorders has its origins in a series of (misguided) experiments of an Australian psychiatrist named John Cade (cf., Snyder, 1986). Although the rationale was wrong, the clinical results proved to be very effective.

Lithium is still a dangerous drug, but it can be used successfully when care is taken to monitor and manage the serum levels of sodium (and lithium). The drug is very effective in reducing and preventing manic behavior. In cases of bipolar disorders of cycling manic depression, the drug is seems to eliminate *both* aspects of the mood disorder. It appears that the depressive phase of the disorder is largely the result of the preceding manic phase. The stabilizing effects of the lithium treatment directly controls the mania and indirectly controls the depression (see Figure 6-15).

The manic behavior may reflect a high level of noradrenergic activity. Behaviorally, this phase is characterized by excessive talking, flights of ideas, excessive and sustained levels of activity, and sometimes prodigious physical and mental accomplishments. When patients "come down" from this phase, the mood may not stop at the normal level, but more typically may continue, dropping into the depths of depression. It is as though the manic behavior continues until the neurotransmitter systems are depleted and unable to continue supporting the behavior. In this regard it should be noted that unipolar mania is rare.

E. BEHAVIORAL APPROACHES

Stress and Neurochemistry

All of the therapeutic approaches discussed above pose dangers to the depressed patient. These are most obvious in the case of ECT. The dangers of drug therapies may be less obvious, but there are very real cardiovascular side effects which become even more salient when one considers the delayed and inconsistently beneficial effects of the drugs. In the long run, the major contribution of all of these therapeutic approaches may be the fact that they have helped to shed light on the underlying

mechanisms of depression. The real "cure" for many patients suffering from depression may lie in behavioral treatments that are designed to change the neuropharmacological conditions that have led to the symptoms of depression.

Stamping in failure

Any successful behavioral treatment of depression must take its cues from both the behavioral symptoms of depression and from an understanding of the effects of environmental interactions with the neurochemistry of the reward system. The experimental conditions that were used in Weiss' experiments (outlined above) were specifically chosen to produce a rapid dysfunction of the noradrenergic transmitter systems. The inability to control noxious stimuli is certainly a major contributor to this effect.

The dramatic impairments of behavior that are triggered by environmental conditions become even more impressive when viewed in the context of related behavioral histories. In the initial experiments of Overmeir and Seligman (1967), the learned helplessness effect had an interesting aspect that has not been generally viewed as a central feature of the phenomenon. As long as the dogs were tested in the shuttle-box within 24 hours after the Pavlovian conditioning, they showed the typical learned helplessness effect and would continue to show this failure to respond in the shuttle-box even when tested again weeks later. However, if a delay of 48 or 72 hours was interposed between the Pavlovian and instrumental conditioning phases, the dogs acquired the shuttle-box normally. Thus the debilitating effects of the Pavlovian conditioning experience were transient in nature.

In a related experiment, Anisman and Sklar (1979) have shown that the neurochemical systems of rats will recover rather quickly from a single session of exposure to stressful electrical shocks. Rats that received 60 shocks showed a transient decline in norepinephrine levels, but after 24 hrs, their norepinephrine levels were indistinguishable from that of control animals that had received no shocks. However, these animals were much more vulnerable to stress than the controls. When both groups of animals were given 10 additional shocks, the control rats showed only a small, transient effect, whereas the previously shocked animals showed a precipitous and more long lasting decline in norepinephrine levels.

In each of these examples, exposure to failure renders these neurochemical systems more fragile and they become increasingly vulnerable to environmental influences (see Fig. 6-16).

Positive effects

The picture becomes a little more complicated, but a little more hopeful, when less severe stressors are used. Weiss and his coworkers (e.g., 1981) have found that repeated exposure to mild stressors may actually have beneficial effects. This type of repeated exposure raises the levels of the enzyme tyrosine hydroxylase in neurons that manufacture and release norepinephrine. This seems to be a specific effect, because the enzyme is not increased in cells that release dopamine, nor is the comparable enzyme of synthesis (tryptophan hydroxylase) increased in neurons that release serotonin. It would appear that the repeated exposure to mild stressors produces a tonic change in neurochemistry that may allow the organism to better cope with stressors that are encountered in future situations.

Reward and Neurochemistry

Another series of experiments brings us back into the more positive aspects of the reward system. In a particularly clever set of experiments, Seiden and his associates have shown a relationship between neurochemistry and interaction with a rewarding environment (Seiden, Brown and Lewy, 1973). Rats that are deprived of water show a slight decrease in norepinephrine levels. If the rats are given free access to a drinking tube, they will replenish their water deficit and a modest increase in norepinephrine levels can be observed. However, if the rats are allowed to rehydrate by pressing a lever that delivers the water as discrete rewards, there is a large increase in norepinephrine levels (see Fig. 6-17). Thus, the direct physiological effects of dehydration and rehydration are minimal, but the insertion of behavioral reward into this sequence has a strong positive influence on the neurochemistry of the noradrenergic systems that have been implicated in the disorder of depression.

These results may also be related to the so-called "freeloader" experiments in which rats given a choice between free (noncontingent) food and food that is contingent upon pressing a lever will frequently choose the option of working for the pellets. Work ethics and social implications aside, these results suggest that the interaction with a rewarding environment is a positive feedback situation that makes it more rewarding to interact with the environment.

The False Perception of Control

Are the symptoms of depression caused by a dysfunction of the reward system, or does the lack of behavior that characterizes depression result in the atrophy of the reward system? Lauren Alloy, working in Solomon's laboratory, developed the intriguing idea that individuals who suffer from depression may not recognize the effectiveness of their own behavior (cf., Solomon, 1980; Alloy & Abrahamson, 1982). In other words, they might be exposed to the same rewards, but because of some deficit, fail to fully recognize the rewards. This idea was investigated in a series of experiments that used college students as subjects. These were not clinical patients. Rather, the students were selected on the basis of their scores on a questionnaire that assessed symptoms of depression. The two ends of the distribution formed the "depressed" and "non-depressed" groups of subjects. These subjects were tested on a sort of computer game in which they attempted to control a light. The actual degree of control ranged from 0-100 percent. Alloy's theory was that the depressed subjects would consistently underestimate the degree of control that was actually present. However, these subjects were very accurate in their estimates. Surprisingly, it

was the normal (non-depressed) subjects who were inaccurate: They consistently overestimated the degree of control! These results suggest that the reward system has a built-in bias to "recognize" control even when it does not exist. This perceived control almost certainly has the same tonic effects on the neurochemical systems as real control. This systematic bias should not be viewed too suspiciously, because such errors are rather commonplace within the nervous system. One of the recurrent features of design within the sensory systems is an organization that exaggerates borders, color differences, frequency differences, and other features of the environment. It is not unreasonable to assume that the system that interprets our control over the environment also presents us with little white lies about the nature of the world around us.

The challenge to therapists is to develop situations that immerse the depressed patient in control. It probably matters little whether the control is real or perceived, or whether it serves a genuine biological need or the trivial manipulation of a monster on a computer screen. The behavioral approaches will not always be successful. They will sometimes need to be administered in conjunction with drug therapies or even with the more drastic approaches of electroconvulsive therapy or surgery. It seems clear, however, that the breakdown of a neurochemical system that interacts so richly with behavior should be treated with behavior whenever possible.

F. SUMMARY

Principles

1. The learned helplessness phenomenon has been used as an animal model for depression.

2. Learning that behavior is ineffective in one situation can generalize to other situations where the behavior actually has an effect.

3. The reversal of depression with the MAO inhibitor, iproniazid, provided the first important link between depression and the catecholamines.

4. Rewards appear to be mediated by catecholamine fibers that lie in the medial forebrain bundle.

5. Acute episodes of stress lower the level of catecholamines in the reward system.

6. These short term behavioral treatments can lead to long term changes via neuromodulation.

7. The treatment of depression is complicated by the cyclic nature of the disorder, the dangerous side effects of the available drug treatments, and individual differences in response to the drugs.

8. The MAO inhibitors appear to facilitate the activity of the catecholamine systems by slowing the metabolism of these compounds. The tricyclic drugs appear to interfere with the reuptake of

catecholamines. It remains unclear whether these biochemical actions account for the clinical effects of the drugs.

9. The metabolites of catecholamines (e.g., MHPG) and of serotonin (e.g., 5-HIAA) may serve as biochemical markers to aid in both the diagnosis and treatment of the various forms of depression.

10. The long therapeutic delay of the antidepressant drugs suggests that they trigger neuromodulatory changes rather than directly ameliorating the condition.

11. Bipolar depression frequently responds well to lithium treatment, possibly because of the drug's ability to prevent catecholamine depletion by preventing the manic phase of the disorder.

12. Electroconvulsive therapy produces an almost immediate reversal of depression as well as an increase in tyrosine hydroxylase levels.

13. Behavioral therapies are effective not only in changing the patient's interpretation of the environment, but also because they are likely to reverse some of the neurochemical changes that provide the foundation for depression.

Terms

5-HIAA

6-OHDA

ACTH

Anterior cortex

Autoreceptors

Biochemical marker

Bipolar depression

COMT

Contingency

Cortisol

Dexamethasone suppression

Electroconvulsive therapy

False transmitter

Free operant

Iproniazid

L-DOPA

Learned helplessness

Lithium

Locus coeruleus

MAO inhibitor

MAO isozymes

MFB

MHPG

Neuromodulation

Norepinephrine

Reserpine

Reward system

Sidman avoidance

Tetrabenazine

Triad design

Tricyclic compounds

Tyramine

Tyrosine hydroxylase

SCHIZOPHRENIA AS A MODEL OF DOPAMINE DYSFUNCTION

SCHIZOPHRENIA AS A MODEL OF DOPAMINE DYSFUNCTION

A. INTRODUCTION

One of the defining characteristics of advanced organisms is the ability to make flexible, yet adaptive responses to environmental stimuli. These stimuli may arise from within the organism or impinge upon it from the outside. The resulting myriad of stimuli ranges in salience from the barely noticeable to the intense. The stimuli in the intense range are usually considered to be biologically significant, whether they originate within the organism or are encountered in the outside environment.

At any given moment, the organism is likely to be faced with many stimuli that could be acted upon, but in reality only a few become the targets of behavior. Psychologists have conceptualized this process as a system of *drives* and *rewards*. The particular combination of stimuli that arises from the outside world and from the physiology of the organism triggers brain activity that has two major effects: It *energizes* behavior and *directs* behavior. For example, if an individual has gone for several hours without food, the stimuli arising from inside the body produce an effect which can be labeled hunger. These stimuli may be intensified by external cues such as the position of the hands on a clock, a television advertisement for junk food, or other food related items. There will be an increase in activity, and, given the appropriate circumstances, this activity will be directed toward food items. The consumption of food is said to be rewarding, and reduces the stimuli that initially energized the search for food.

The schema outlined above reflects the operation of the reward system, and as discussed in previous chapters, this system is believed to rely upon activity of catecholamines in fibers that arise from cells in the midbrain and project to various forebrain regions. Normally, this system organizes behavior in a systematic fashion that not only enhances the organism's ability to survive, but also makes it easier for psychologists to formulate laws of behavior. When this system fails to operate normally, the behavior of

the affected individual strays outside of the normal expectancies, and some sort of label is attached to indicate a problem in behavioral adjustment. The behavior of the individual may be energized at inappropriate times (or at an inappropriate level), or it may be directed toward goal objects that are inappropriate or even nonexistent. Let us consider a couple of examples before going into the main body of this chapter.

One of the behavioral disorders that has been linked to the reward system both in its symptoms and its treatment is hyperkinesis or hyperactivity. This disorder typically appears in early childhood and is considerably more likely to afflict boys than girls. These children rarely require institutionalized care, but present tremendous challenges to teachers and parents. The disorder is characterized by impressive and unceasing physical activity. The child typically begins the day early with loud interactions with parents and siblings, running through the house, bumping into things and breaking them, getting into fights, spilling food, and so on. In school, the child distracts others by refusing to stay seated, fails to complete projects, and generally performs poorly. Bedtime is no exception to the exaggerated activity, and several tuckings in are likely to be required before both child and caretaker collapse into sleep.

When placed in the context of the reward system outlined above, hyperkinesis certainly can be viewed as an increase in the energizing aspect of drives, but it might also be characterized as a lack of directed behavior. Indeed, the disorder is now officially referred to as attention deficit disorder. It is in this regard that one of the most paradoxical and effective treatments comes into the scene. The behavior of these children would seem to require no further stimulation, yet one of the most effective treatments is the administration of amphetamines. The amphetamines are known to facilitate the functioning of neurons that release catecholamines, and have been shown to enhance rewards or to serve as rewards themselves. The most popular interpretation of the effectiveness of amphetamines in treating hyperkinesis is that the treatment enhances reward and provides more direction to the behavior. In both hyperkinetic and normal children (and adults for that matter), amphetamines can increase the attention span, which tends to normalize the behavior of the hyperkinetic children (e.g., Zahn, et al, 1980).

Autism is another disorder that may involve a dysfunction of the reward system, although the links have been less direct than in the case of hyperkinesis. The disorder is characterized by withdrawal from other individuals and a failure to respond to many external stimuli. Stereotyped behaviors are common, and may include sitting and rocking, manipulating an object over and over, or insisting that specific routines (e.g., going to bed) be followed in ritualized detail. This is a very serious and complex disorder that includes language difficulties and severe learning disabilities, but at least some of the symptoms can be related to the reward system. These aspects of the disorder are virtually the mirror image of hyperkinesis. The energy of the behavior is below normal and narrowly directed to only a few stimuli, while ignoring many other stimuli that are relevant to the normal individual. Although there are no particular drug therapies that are useful, there is a link to the reward system through some of the animal experimentation that was discussed in previous chapters. In particular, some of the work of Harlow and associates (e.g., Harlow and Suomi, 1971) showed that isolation of infant monkeys from both their mother and their peers produced stereotyped motions, withdrawal from other individuals, neglect of external stimuli, and (placing it in the context of our present discussion) large decreases in brain

norepinephrine levels.

One of the current views of this disorder, that it may involve an excess of endorphins, was put forth by Kalat (1978) solely on the basis of behavioral symptoms. Consistent with this model is the observation that treatment with naloxone, a blocker of the endorphins, can ameliorate the symptoms in some cases. The close interaction between the endorphin systems and dopamine systems may, ultimately, form the foundation for a better understanding of autism.

B. CLASSIFICATION OF SCHIZOPHRENIA

The schizophrenic disorder has played a pivotal role in the development of a system of classification of behavioral disorders. It has long been the prototype of the group of serious disorders of thought processes that are termed psychoses. Less serious disorders of life adjustment are termed neuroses. These are old terms, and their derivations seem curiously reversed in the light of current knowledge. The term psychosis means disease of the mind, which seems reasonable enough, except that the term neurosis means disease of the neuron, implying a more physical basis for the less serious behavioral disorders.

The terms neurosis and psychosis reflect, in their original meaning, a related dichotomy of classification, namely, *organic* vs. *functional*. These opposing views of the roots of mental disorders go far back into history (as cited by Stein & Wise, 1971): St. Augustine (ca. 400 AD) took the functional viewpoint and asserted that "There are no disorders that do not arise from witchery, and hence from the mind." More recently, Thudicum (1884) made the interesting proposal that "...many forms of insanity are caused chemically by poisons fermenting within the body." These are not idle philosophical notions, because in a very real sense, they set the course for effective treatment. In the pure sense, one would expect behavioral methods to work for functional disorders, while chemotherapeutic methods might be better for organic disorders. These assumptions are clearly overstated, because of the known interactions between behavior, environment, and brain, but they nonetheless provide broad suggestions for the types of treatment that are most likely to succeed.

Historically, there have been some major successes in the treatment of severe disorders based on an understanding of the organic causes. The mental deterioration that accompanies the advanced stages of syphilis has been substantially controlled by penicillin. Pellagra, a disease which starts as a skin disorder and eventually results in severe mental deterioration, can be controlled by correcting the niacin deficiency of the diet.

Perhaps the most dramatic success has been in the treatment (though not the cure) of schizophrenia. This disease afflicts more than one percent of the population and is both chronic and progressive. It accounts for more than half of the resident mental hospital population. As indicated in chapter 4, there was a steady climb in the number of permanently institutionalized patients in mental hospitals during the early decades of this century. This dramatic rise was primarily a reflection of the increase in population, perhaps inflated a bit because of increasingly favorable attitudes toward institutionalized treatment.

Schizophrenia was a major contributor to this patient population, and there seemed to be no end in sight. Then, after the mid-1950's, the number of chronically hospitalized patients dropped precipitously. This reduction can be attributed to the development of new drugs, the most important of which was chlorpromazine. (Unfortunately, many of these patients do not receive adequate care outside of institutions and fall into settings, such as living on the street, where they no longer take the drug and relapse into the full symptoms of the disease.)

As indicated in chapter 4, chlorpromazine was developed by the French physician, Laborit, as an autonomic stabilizer. The impact of this drug as an antipsychotic agent went far beyond anybody's expectations. The drug allowed the patients to return to the care of their families, or to less continuous care facilities. Even disregarding the tremendous reduction in human suffering, the role of chlorpromazine can hardly be overemphasized. In 1965, chronic hospitalization cost an estimated $7,000 per year. Today's costs may be more than ten times that value. The yearly financial savings can be conservatively estimated in the hundreds of millions of dollars!

The effectiveness of chlorpromazine in the treatment of schizophrenia set the stage for the development of realistic models of organic causes of mental disease--causes that are based on known functions of the neuronal physiology. This chapter will trace some of the highlights of the search for a plausible, if not valid neuronal model for schizophrenia. The groundwork for this search lies not only in the analysis of drugs such as chlorpromazine, but also in a more careful consideration of the major symptoms of schizophrenia.

The term schizophrenia has undergone many misinterpretations since it was first introduced (cf., Bleuler, 1950). The disorder is so common and the symptoms are so bizarre that the terminology has become a part of the layman's vocabulary. The most unfortunate misinterpretation is the translation of the term schizophrenia into split personality. Although the root of the word does refer to a splitting, Bleuler saw the disorder as a fragmentation of normal processes: "Thoughts, feelings and actions are not related and directed by any unifying concept or goal...a fragmentation of the central integrative process." It is precisely this lack of directed or unified behavior that Bleuler used to define the primary symptoms of schizophrenia:

- Disturbance of thought patterns
- Disturbance of affective reactions
- Autism or withdrawal

These primary symptoms, individually and collectively, represent a loss of contact with reality. The patients show very atypical responses to their social situations. They commonly make up words and sentence structures, their responses to verbal communication may bear little or no relationship to the

topic at hand, and their behavior is frequently at odds with the environment around them. Their affective reactions are inappropriate to the situation, with laughing or crying at the "wrong" times, etc. In later stages of the disorder, the affective disturbance is characterized by a profound inability to experience pleasure. In all of these situations, the patients are likely to show a withdrawal from the people around them, and in a sense, produce and respond to their own stimuli rather than to the outside world. This withdrawal also accounts for the rather curious fact that most people do not know a person suffering from schizophrenia. Yet, the incidence of schizophrenia is almost as great as the incidence of twins, and most people know several sets of twins.

The primary symptoms outlined above are frequently accompanied by one or more secondary symptoms. The symptoms were termed secondary because they are not necessarily present in all cases of schizophrenia. Ironically, these symptoms are the ones that are commonly portrayed in literature as prototypes of mental illness, so there is a natural tendency to assign greater importance to these symptoms in defining schizophrenia. These secondary symptoms include:

- Hallucinations
- Delusions
- Paranoia

The secondary symptoms also reflect a loss of contact with reality. The hallucinations are usually auditory, and may include voices that provide instructions, criticism, or praise-- but with little or no basis in fact. Delusions of identity may occur, with patients adopting the identity of a famous individual, or delusions of unique powers. On the other side of the coin, they may have delusions of persecution, or feelings that they are being controlled by unique powers. Given the bizarre nature of their behavior, some of the paranoia that these patients may experience will be real. People, in fact, will talk about them and be suspicious of them. Yet, the paranoia of some of these patients is as extreme as it is bizarre, and clearly is pathological in nature.

The florid symptoms of schizophrenia lead naturally to the question, What happened to this person to cause these symptoms to develop? In many cases, it may be possible to find environmental factors that contributed to the disorder, but the evidence is very strong that the disease of schizophrenia has a firm biological (organic) basis which, at the very least, predisposes the individual to develop the symptoms.

C. EVIDENCE FOR BIOLOGICAL BASES OF SCHIZOPHRENIA

Distribution of Occurrence

One of the best indicators for a biological basis of schizophrenia is the independence from culture. The disorder is represented in all cultures (be they primitive or industrial, permissive or strict, 1920's or 1980's) at a rate of about one or two percent. (This rate may sound low, until you calculate the real numbers for your home town or consider that there should be something on the order of 400 cases in Bangor, Maine.)

There is also a tendency for the disorder to appear in early adulthood, to preferentially afflict those with an ectomorphic body type, and (curiously) to be much less likely in those suffering from rheumatoid arthritis or Parkinson's disease. None of these factors would seem to be important in terms of environmental events that might precipitate the disease.

Genetic Patterns

A second line of evidence for a biological basis of schizophrenia is the strong genetic pattern of occurrence (cf., Heston, 1970; Nicol and Gottesman, 1983). The strongest relationship occurs between monozygotic (identical) twins. In cases in which one member of a monozygotic twin pair has schizophrenia, there is a 46% chance that the other member also suffers from schizophrenia. Thus, in about one half of the cases, one of the twins does not develop schizophrenia, even though the genetic makeupis identical; but pathology is still the norm, since only about 13% are judged to be normal. Dizygotic or fraternal twins, like siblings, share about one half of the genetic information. When a sibling or one member of a fraternal twin pair has been diagnosed as having schizophrenia, the other member bears about a 10-15% chance of being afflicted with the disease. Similarly, the child of a schizophrenic parent has a likelihood of becoming schizophrenic that is about 15 times that of the general population. Although the relationship is not perfect, there clearly is a high correlation between the closeness of genetic relationship to a schizophrenic patient and the probability of developing the disorder (see Fig. 7.1).

A word of caution is in order concerning the interpretation of the experiments that purport to show the relationship between genetics and the incidence of schizophrenia (or any other characteristic). There is also a strong correlation between genetic relationship and environment. If the home environment causes one child to become schizophrenic, would it not also be likely to cause siblings (or especially a twin) to become schizophrenic? Should one be surprised that a parent suffering from schizophrenia raises a child with similar characteristics? Although these are valid criticisms, there are a few experiments that provide counter-arguments. In some cases, it has been possible to find diagnosed schizophrenics who have twins or siblings that have been raised since birth or early childhood in foster homes. The results of these studies show relationships that are comparable to those described above. The likelihood of developing schizophrenia is more predictable based on the mental health of the biological mother than on that of the foster mother.

One of the most spectacular studies of the genetic and environmental influences on schizophrenia is that of the Genain quadruplets (Rosenthal, 1963). These quadruplet girls were the subject of intense study over a period of many years. Although it was impossible to eliminate all uncertainty, it seemed likely

that they were monozygotic. One of these children developed schizophrenic symptoms at an early age. All three of the remaining quadruplets developed symptoms ranging from frank schizophrenia to schizoid tendencies during later years. The age of onset and the severity of the symptoms were related to birth weight, the lightest birth weight showing the earliest and most severe symptoms. The father of the girls and his mother both suffered from schizophrenia. The mother of the girls had some problems (not the least of which were a schizophrenic husband and quadruplet daughters!), but was not diagnosed as schizophrenic. This case study is probably a perfect example of the conclusions that should be drawn about the role of genetics and environment in schizophrenia: It seems obvious that one's genetic heritage can provide a strong predisposition toward schizophrenia, but whether or not the disease is manifested may be determined by other factors such as the home environment, the prenatal environment, dietary factors, and even other genetically determined characteristics.

Drug Effects and Schizophrenia

When Laborit developed chlorpromazine, his major motivation was to find a drug that would stabilize autonomic activity. In particular, one that would stabilize the stress response centrally, blocking the autonomic nervous system's reflection of the brain's interpretation of the response. The drug had such profound effects in the reduction of the stress response that it was rather quickly adopted for the treatment of patients who were suffering from anxieties arising from real or imagined stressors in their lives. In the language of the times, it was a *major tranquilizer*.

Chlorpromazine, like any other drug, has multiple effects, and some of these effects are troublesome during the course of therapy. The presence of these so-called "side effects" almost always leads to a search for related compounds that might share the parent drug's therapeutic effectiveness while diminishing the undesirable side effects. Over the years a fairly large number of related phenothiazine compounds were introduced into the clinic. Although none of these compounds was demonstrably better than chlorpromazine in the treatment of schizophrenia, the large scale clinical use of the phenothiazines set the stage for determining the most likely mode of action of these compounds-- namely, the blocking of dopamine receptors. The remarkably close correspondence between clinical potency and affinity for the dopamine receptors has already been seen in Figure 4.11. Correlations can be misleading, but the orderliness of these data lead, almost inescapably, to the conclusion that the phenothiazines produce their beneficial effects in schizophrenia by blocking the dopamine receptor.

The idea that schizophrenia is related to a dysfunction of the brain's dopamine system is consistent with several types of observations of drug actions. One line of evidence concerns the specificity of the phenothiazines in the treatment of schizophrenia. As we saw in Chapter 4, both the phenothiazines (e.g., chlorpromazine) and the benzodiazepines (e.g., Librium) have sedative or anxiety reducing properties. Despite this similarity in the treatment of these symptoms, Librium and related compounds are not effective in the treatment of schizophrenia. The benzodiazepines have little or no effect on dopamine receptors. Furthermore, chlorpromazine and related compounds seem to act rather specifically on the primary symptoms of schizophrenia, rather than the secondary symptoms (see above). The drugs that are most effective in treating these primary symptoms also tend to be the most likely to produce side effects

that are similar to Parkinson's disease, a movement disorder that has been attributed to a deficiency of dopamine in certain brain areas.

A second line of evidence that supports the link between primary symptoms of schizophrenia and the dopamine system are the effects of hallucinogenic drugs. Compounds such as LSD produce hallucinations in both schizophrenic and normal individuals. However, these drug effects are usually distinct from the schizophrenic symptoms, and the schizophrenic patients recognize the hallucinations, but do not attribute them to their illness (cf., Hollister, 1962). These observations suggest that the hallucinations, which Bleuler considered to be a secondary symptom of schizophrenia, may involve non-dopamine systems that are not involved in the primary disorder.

The effects of amphetamine, a drug which stimulates neurons that release dopamine (as well as those that release norepinephrine), also strengthen the case for dopamine involvement in schizophrenia. In normal individuals, small dosages of amphetamine produce psychomotor stimulation. Repeated high dosages of amphetamine produce greater stimulation, and in some cases, a breakdown that is indistinguishable from acute paranoid schizophrenia. As it turns out, the diagnostic distinction between an amphetamine overdose as opposed to a schizophrenic breakdown is not immediately critical. In either case, the treatment of choice is the administration of chlorpromazine or some related phenothiazine. This line of argument can be extended by observing the effects of amphetamine on schizophrenics. Low doses of amphetamine that would produce only a mild psychomotor stimulation of a normal individual, produce a strong and specific activation of the primary symptoms of schizophrenia (cf., Janowski et al, 1972). Unlike the effects of the hallucinogenic drugs noted above, the patient attributes the effects of the amphetamine to a worsening of the schizophrenic condition. Again, phenothiazines are effective in reducing these symptoms.

D. BIOLOGICAL MODELS OF SCHIZOPHRENIA

Searching for a Chemical Label

There have been hundreds of futile and misguided attempts to determine the biochemical basis of schizophrenia. Many of these experiments took the statistically unlikely approach of trying to find a unique chemical in the blood, urine, saliva, or some other body fluid of the schizophrenic patient. There were many positive results, but nearly all of these turned out to be false leads, with the apparently unique chemical substance being unrelated to schizophrenia, and instead, being the result of differences in physical activity, institutional diet, by-products of medications, or the amount of coffee consumed. This is clearly a needle in the haystack approach. Given the thousands of body chemicals, the likelihood of choosing to assay the one (if there is one) that is a unique marker for schizophrenia would be very small indeed.

A much more logical and positive approach to trace the causes of schizophrenia is to base the search on behavioral and neurochemical systems that are known to be involved in the disease of schizophrenia. A

model of schizophrenia that is based on the function of a particular set of neurons would be much more plausible than one simply based on the presence or absence of some chemical.

The DBH Model

Rationale

One of the most appealing neuronal models of schizophrenia is the so called "DBH Model" (dopamine beta hydroxylase) that was put forth a number of years ago by Stein and Wise (1971). The model is almost certainly wrong in at least some of its details, but it is exemplary because of its testability, its basis on known physiological processes, and the relationship of these processes to behavior. We will trace this model in some detail because portions of it may be correct, and because it serves as an excellent model of the type of approach that must be taken to find the roots of any organically based disorder of behavior.

The initial focus of the Stein and Wise theory was on the behavioral aspects of schizophrenia. The lack of organized and directed behavior, the inability to experience pleasure, and the withdrawal from the external environment all pointed to a dysfunction of the reward system. But what could be causing this deterioration of these neurons? Could it be that Thudicum had been correct many years ago when he suggested that insanity might be caused by some poison, fermented within the body? If so, what might the characteristics of that poison be? Given the clinical progression of schizophrenia, several limitations would have to be placed upon such a poison. It would have to be produced more or less continuously over the course of many years to account for the progressive deterioration of the behavior of schizophrenics. It would have to act rather specifically on certain populations of neurons to account for the primary symptoms of schizophrenia. It would have to be more or less immune to tolerance, or the body would quickly adapt to it, causing a short term disorder. Finally, it is likely that the substance would be present in relatively small quantities, or it would have been captured in the net of one of the many biochemical studies that have been done. What sort of a chemical might this be?

Stein and Wise proposed that the disease of schizophrenia might be caused by low levels of 6-hydroxy dopamine (6-OHDA) circulating in the bloodstream. As indicated in previous discussions (cf., Chapter 5), 6-OHDA is a powerful and specific neurotoxin that enters the terminals of catecholamine bearing neurons and physically destroys them. As shown in Figure 7.2, the administration of 6-OHDA to rats causes them to stop responding to the rewarding effects of brain stimulation, mirroring the inability of schizophrenics to respond to pleasure. Furthermore, these effects can be blocked by chlorpromazine and related phenothiazines. The most likely mechanism for this protective effect is the blockade of the specific receptors that are involved in the reuptake mechanism of these neurons. The inability of the 6-OHDA to enter the cells exposes it to other metabolic process that inactivate it, while protecting the cell from the destruction that would ensue if the 6-OHDA were allowed to enter. A final feature that mimics the disease of schizophrenia, is that the rats that have been poisoned with 6-OHDA show waxy flexibility, a bizarre dysfunction of the motor system that allows them to be "molded" into postures that are sustained for long periods of time.

But are these symptoms more than coincidental? Is it reasonable to suspect that the disease of schizophrenia is caused by a neurotoxin that was invented in a biochemist's test tube? If so, what would cause one or two percent of the population to produce the substance while the remaining population does not?

Despite the superficial similarities between the effects of 6-OHDA and the symptoms of schizophrenia, the model would seem to be implausible without some mechanism for the body to produce the neurotoxin. The suggestion of a mechanism by Stein and Wise was both ingenious and insightful. They proposed that the root of the disorder was an enzyme deficiency.

DBH as a rate limiter

Figure 7.3 shows the normal sequence of reactions in the formation of the catecholamine neurotransmitters. Each step of the sequence is assisted by a specific enzyme which, as a rule, speeds up the reaction. One of the characteristics of a sequence of biochemical reactions such as this is that the overall rate of transformation of the initial compound into the final product (in this case, the conversion of the amino acid tyrosine into norepinephrine) can proceed only as fast as the slowest step. By analogy, if water is being poured into a bucket through a series of funnels, the bucket will fill only as fast as allowed by the smallest funnel. In some cases, a sequence of biochemical reactions might be limited by the amount of compound available for conversion, or by the amount of enzyme present at one of the steps, or by the speed of the enzyme. In this particular example, it has been established that the so-called rate limiting enzyme is at Step 1, the conversion of tyrosine into DOPA (dihydroxyphenylalanine). The enzyme is called tyrosine hydroxylase, which describes the nature of the chemical action that it facilitates.

The location of the rate limiting reaction at Step 1 means that in the normal sequence of events, this step governs the remainder of the sequence. As in the case of an assembly line, the faster activity at Step 2 converts all of the DOPA into DA and must "wait" until additional DOPA is formed. Likewise, Step 3 is limited by the amount of DA that is formed. These phenomena are confirmed by biochemical experiments which show that modest increases or decreases of the enzymes at Steps 2 and 3 have no effect on the sequence of reactions. By contrast, small changes in the activity of tyrosine hydroxylase are reflected in the overall conversion of tyrosine into norepinephrine (see Fig. 7.4).

Stein and Wise proposed that schizophrenia involves a deficiency of the enzyme in Step 3, dopamine beta hydroxylase or DBH. If this enzyme is present in smaller than normal quantities, it can become the rate limiting enzyme and set the stage for the sequence of events shown in Figure 7.5. According to this scheme, tyrosine would be converted to DOPA, all the available DOPA would be converted to dopamine, but the dopamine would be present in excess because of an inability to rapidly convert it into norepinephrine. It is this excess of dopamine that allows abnormal chemical conversions to take place. The availability of dopamine, exposes it to the action of other enzymes. The details of these enzymes are not important in the present context, but Stein and Wise presented biochemical pathways that could

convert dopamine into 6-OHDA. Once the body has formed this neurotoxin, it could be taken up by the neurons that normally release norepinephrine or dopamine, and the cells would be destroyed in the same manner as if the drug had been administered by a hypodermic needle. Thus, the metabolic machinery is there for Thudicum's poison to be "...fermented within the body," and Stein and Wise have shown how the machinery might be put into action when normal pathways of neurotransmitter production have gone awry.

There is also another line of evidence that can be supported by the DBH hypothesis. As a result of some of the earlier biochemical sleuthing, it was determined that many patients suffering from schizophrenia have a characteristic odor in their sweat. Rats, dogs, and even humans can be trained to discriminate between odors derived from the sweat of schizophrenics and that derived from normal subjects (Smith et al, 1969). This substance has been isolated and identified. Curiously, the substance can be formed in a few steps by beginning with 6-OHDA and proceeding through a series of biochemical reactions that can take place in the human body.

The DBH model of schizophrenia has been strongly criticized. The naysayers point out that 6-OHDA per se has not been found in schizophrenics. Nor has it been demonstrated that the 6-OHDA is the substrate that forms the identifiable odor substance. When scrutinized in fine detail, some of the similarities of the effects of 6-OHDA on rewarded behavior in rats seem only remotely related to the symptoms of schizophrenia. The biochemical assays of the levels of DBH in the brains of schizophrenic patients (performed at autopsy; Wise and Stein, 1973) showed lowered levels, but the results were not as dramatic as one might like. The model has, however, served as a focal point of discussion and of the design of experiments over the years. It is also of historical importance, because even if it does not turn out to be an accurate model for the disease of schizophrenia, it is an admirable model for models. It is precisely this type of neurological model, based on variations of firmly established phenomena, that will eventually unlock the mysteries of schizophrenia. The next section will discuss some additional proposals for the nature of schizophrenia. Some of these oppose the DBH theory, others are consistent with it, but none is as global in its approach.

Other Dopamine Models

Metabolic pathway theories

Whether or not the primary neuronal deficit in schizophrenia is a deficiency of DBH, it seems likely that some disorder of dopamine metabolism is involved. The detailing of this change in metabolism has remained elusive because of several problems: Foremost is the problem of diagnosis, with "schizoid" symptoms presenting themselves in a variety of mental disorders that may not turn out to be true schizophrenia, as well as the likelihood that several different forms of schizophrenia may exist (we shall return to these problems later in the chapter). The progressive nature of schizophrenia also presents a problem because some of the biochemical markers for the disorder actually may be more salient during the early stages than after the disease has become more serious. Finally, there remains the simple fact that these patients require care, and it is difficult for researchers to find a patient population that has not

been treated with phenothiazines or other drugs that are known to produce large changes in the very systems being investigated. Despite these and many other problems, the research findings have shown a continuous, if not entirely coherent, thread of evidence for impaired function of the dopamine systems.

Wise and Stein reported in 1973 that the brains of schizophrenic patients had somewhat lower levels of DBH than normal persons of the same age and sex who had died in car accidents. More recently, this biochemical difference has reemerged with the development of techniques that are more sensitive than relying on autopsy data. Some schizophrenic patients have lower than normal levels of DBH in the cerebrospinal fluid, while others do not. Those who show this deficiency tend to respond better to phenothiazine treatment and also appear to have brain atrophy, as demonstrated with computer tomography techniques (Sternberg et al, 1982; van Kammer et al, 1983). Not only are these data consistent with the original hypotheses of Stein and Wise, but it has also been shown that phenothiazine activity can be enhanced by simultaneously administering alpha methyl tyrosine, a potent inhibitor of the normal rate limiting enzyme, tyrosine hydroxylase. This treatment, in effect, would allow tyrosine hydroxylase to regain its status as rate limiter, even in the face of lowered DBH levels.

A dysfunction of dopamine cells would also be expected to result in different levels of catecholamine metabolites by changing the relative involvement of the various enzyme pathways (cf., Fig. 6.13). One product that has been linked repeatedly with schizophrenia is (HVA) homovanillic acid, although the results are not as consistent as one might hope. Pickar and associates (1984) found elevated levels of HVA circulating in the plasma of schizophrenia patients. Phenothiazine treatment produced a gradual reduction of HVA levels over a 3- to 6-week period, and the improvement of schizophrenic symptoms showed a comparable delay. These data are very impressive, but it should also be noted that other investigators have reported normal HVA levels (e.g, van Kammer et al, 1983) that may increase with phenothiazine treatment (e.g., Bacapoulos et al, 1979). One possible resolution of this apparent discrepancy is that one group measured circulating levels of HVA in the plasma, while the other measured HVA levels of brain tissue. These different compartments may, in a sense, represent the same scene from different angles.

Amphetamine and amphetamine-like compounds have also continued to play a role in theorizing about schizophrenia. Phenylethylamine (PEA) has been found to be twice as high in the urine of paranoid schizophrenics than in either non-paranoid patients or the normal population (Potkin et al, 1979). This is interesting not only because low dosages of amphetamine can exacerbate the symptoms of schizophrenia, but also in light of recent findings of neurochemical changes that accompany chronic amphetamine administration. Trulson and Jacobs (1979) administered large dosages of amphetamine to rats over a three-week period. In addition to the expected decline in norepinephrine and dopamine levels, they also found a reduction in serotonin (5-HT) and the related compound, 5-HIAA. Hallucinogenic drugs are also known to interfere with 5-HT and 5-HIAA, and they produce the same abnormal behaviors of limb licking and abortive grooming that were observed in the amphetamine treated animals.

There is little doubt that dopamine metabolism is abnormal in schizophrenia patients, but we may be

dealing with a chicken and egg problem: Is the metabolic change the cause of the disease or does it reflect a reaction to some more primary cause such as a change in receptor number or sensitivity? We turn now to a discussion of some of the research findings on receptors which may help to confirm that the metabolic changes are, in fact, the chicken (or the egg).

Receptor theories

We already have pointed out the powerful interplay between the clinician and the neurochemist in demonstrating the relationship between phenothiazine potencies and their ability to block the dopamine receptor (cf., Fig. 4.11). This relationship has become even more impressive with the introduction of more drugs and the discovery of different dopamine receptor types (D1, D2, and maybe even D3 and D4). The relationship between clinical potency and the ability to block the *D2 receptor* is nearly perfect, while the affinity for the D1 receptor is virtually unrelated to clinical efficacy (see Fig. 7.6). The question then becomes more specific: What does the D2 receptor do? The current evidence is that this receptor is involved in neurotransmitter functions of dopamine that are related both to schizophrenia and to the extrapyramidal motor system. But the key to the importance of the D2 receptor may be its neuromodulatory function rather than direct neurotransmission.

Dopamine receptors appear to mediate both the transient neurotransmitter functions (e.g., depolarization) and the longer term neuromodulatory effects that alter cell metabolism (Figure 7.7). An understanding of these dual effects requires the introduction of a new concept, that of second messengers. The neurotransmitter is the first messenger, and its arrival at the receptor carries the information that the presynaptic cell has been active (in this regard, the receptor on the post-synaptic membrane is now coming to be referred to as the *recognition site*). The recognition site may simply confirm that the presynaptic cell has sent a signal. This information must then be translated into a cellular response. Typically, we think of this cellular response as being short-term in nature, reflected as a depolarization that may initiate an action potential to continue the message on down the line. In other cases, however, the result might be a long-term change in some aspect of the cell's physiology such as a change in the number of receptor sites or a change in the rate of transmitter production or storage. In all of these cases, it appears that second messengers are involved: the recognition site triggers some second event that may alter an ion channel (in the case of typical depolarization) or alter the structures of proteins that are involved in enzyme systems or receptor structures. The two most common second messenger systems are cyclic AMP and the phosphoinositide cycle. Both of these are involved in the changes in protein structure that mediate both short- and long-term changes in the neuron. In this particular example, the interaction of dopamine with the D2 membrane receptor inhibits the second messenger, adenyl cyclase. The adenyl cyclase mediates the conversion of the high energy compound ATP into cyclic AMP. This provides the energy for the formation of protein kinase, which is involved in the phosphorylation reactions for the synthesis of the various enzymes of the cell.

Although this whole process begins to sound a little like the house that Jack built, the end result is that the release of dopamine onto these receptors can control the metabolism of the cell, determining for example, the rate of synthesis of the neurotransmitter (which may or may not be dopamine in this

postsynaptic cell). Returning now to the specific receptor types, the interaction of dopamine with the D2 receptor inhibits adenyl cyclase, while the D1 receptor enhances it. If we assume an excess of dopamine activity in schizophrenia, then the role of phenothiazines is not only to block the depolarizing effects of dopamine on the postsynaptic cell, but also to allow the *metabolic functions* of the postsynaptic cell to return toward normal by interfering with the abnormally high inhibition of the second messenger, adenyl cyclase.

Endorphin contributions

The endorphins (cf., Chapter 7) have also entered the scene in the attempts to provide a biochemical model of schizophrenia. The early reports of the alleviation of schizophrenia symptoms by administering (or blocking) endorphins were probably more enthusiastic than real. But as the understanding of these neuropeptides improve, they will almost certainly play a major role in the treatment of schizophrenia. In addition to serving as neurotransmitters, endorphins have at least two major influences on the dopamine systems: They can modulate the release of dopamine by acting on presynaptic receptors, and they can change the number or sensitivity of dopamine receptors on the postsynaptic membrane by influencing the protein phosphorylation mechanism described above (Volavka et al, 1979; see Fig. 7.8). Some of these effects may be mediated directly by neighboring peptidergic neurons. Others may involve the release of peptides along with dopamine.

But what about Dale's Law of one transmitter per cell? One of the last bastions of simplicity in brain models, this law has been rather thoroughly repealed. Alas. The neurochemical maps of the brain now include a column for coexisting peptides, and the presence of multiple transmitter substances seems to be more the rule than the exception (e.g., Hoekfelt et al, 1984, 1987). It may still be true that only one compound serves the specific neurotransmitter function of changing the polarization of the membrane, but the other ingredients of this synaptic cocktail have important effects on such things as the regulation of release, the sensitivity of receptors, and the long-term changes in metabolic functions of both the presynaptic and postsynaptic cells (Fig. 7.9).

The dynamic synapse

Another important aspect of neuromodulation is the regulation of receptors. Receptors and transmitters are not static entities in the lock and key sense, but rather they are in a state of dynamic equilibrium that has been likened to the concept of homeostasis in other physiological systems. The membranes involved in the release and reception of neurochemicals have a real half-life, which is another way of saying that they wear out and must be continually replaced. We have seen mechanisms for changing the synthesis, release, autoreception, postsynaptic reception, and second messenger effects in the next cell. Normally, these are all orchestrated to meet the current exigencies of a neural system. When this complicated set of controls goes awry, a disease state such as schizophrenia may result.

This dynamic model of the synapse also adds several levels of complexity to the actions of drugs, as we have already seen in earlier chapters. The time course of drug effects may provide a clue concerning the

nature of the therapeutic effect. The phenothiazines have some immediate effects, such as the calming of agitation, but the relief of many of the more definitive symptoms of schizophrenia may not appear for several weeks. This delayed action (see also the discussion of delay of antidepressant drugs) suggests that the effects rely upon long term metabolic changes that are triggered by the drug. One of the more detailed models of the therapeutic effects of phenothiazines has been developed by Bunney and associates (e.g., Bunney, 1984; see Figure 7.10). According to this model, phenothiazines initially block inhibitory feedback, *increasing* DA release. This results in the formation of *more* DA receptors, but postsynaptic activity is eventually blocked (after a few weeks) by a combination of direct phenothiazine blockade and chronic depolarization. The complexity of this model goes well beyond the level of this text, but the principal is of central importance: The therapeutic effects of drugs cannot always be fully appreciated by their simple actions of blocking, mimicking, and other synaptic actions. These actions cause reactions, and the cell systems that are influenced by the drug make long-term changes to reflect the exposure to these effects.

Movement Disorders

Movement disorders have a long history of association with schizophrenia. One of the early observations was the mutually exclusive nature of Parkinsonism and schizophrenia. Each disorder afflicts a sizeable portion of the population and, by chance, one would expect 1-2% of the patients with Parkinson's disease to be afflicted with schizophrenia. Such patients are rare, and some investigators would claim that clear-cut cases are nonexistent. Why? As the understanding of both diseases progressed, dopamine became the focal point of both diseases, with Parkinsonism being characterized by dopamine deficiency and schizophrenia as dopamine excess. More recently, the emphasis has shifted to receptors, with Parkinsonism being linked to too few receptors (perhaps the result of autoimmunity; cf., Chapter 7) and schizophrenia to too many receptors.

Although both diseases are linked to dopaminergic systems, and even to the D2 receptors, the anatomical substrates may be separable (Fig. 7.11). There are two, rather distinct clumps of dopaminergic cell bodies (known to anatomists as A9 and A10) in the region of the pons. The A9 region is roughly equivalent to the substantia nigra, and projects fibers to the striatum via the nigrostriatal pathway, forming the core of the extrapyramidal motor system. In close juxtaposition to this system, fibers from the A10 region (ventral tegmental area) project to various portions of the limbic system and some cortical regions, most of which have been linked to emotional responsiveness and-- when in dysfunction-- to schizophrenia.

We have already seen that the phenothiazines block the D2 receptor, so it should come as no surprise that a major "side effect" of these drugs is an impairment of extrapyramidal functions. In fact, the symptoms produced by these antipsychotic drugs are similar to those that occur in the disease state of Parkinsonism. The short term problems with these side effects are not insurmountable. The dosage of phenothiazines can be adjusted to minimize these effects, and some degree of tolerance appears to develop to the extrapyramidal effects. Furthermore, the extrapyramidal effects can be alleviated by the administration of antimuscarinic drugs, or by choosing a phenothiazine that happens to also have

muscarinic blocking properties. In the long run, however, the prognosis is somewhat bleak. If the neuromodulatory effects triggered by the phenothiazines can gradually reduce the symptoms of schizophrenia, there is no reason to suspect that they would not also gradually produce extrapyramidal difficulties. Indeed, it has been demonstrated that haloperidol produces neuronal sprouting within the nigrostriatal system (Benes et al, 1979), presumably in counter-response to the DA receptor blockade. Clinically, these effects are exhibited as a troublesome and largely irreversible decline in extrapyramidal function which has been labeled tardive dyskinesia (the term tardive referring to the delayed development of the disorder). Tardive dyskinesia is, in some sense, the exact opposite of Parkinson's disease. Most clinicians feel that the risk of progressive motor dysfunction is a substantial, though acceptable, price to pay for the control of the progressive and even more debilitating symptoms of schizophrenia. Unfortunately, there is at present no apparent neurochemical distinction between these two systems that allows specific treatment of schizophrenia: The phenothiazines remain the drugs of (reluctant) choice.

We alluded earlier to the clinical complexity of schizophrenia, a disorder that presents a baffling array of symptoms to the clinician. Furthermore, there are other types of disorders that present symptoms that are also characteristic of schizophrenia. Two of the more notable mimickers of the disorder are amphetamine overdose and the manic phase of bipolar affective disorders. The manic disorders have sometimes been termed schizoaffective, an unfortunate label, because it encourages the prescription of phenothiazines. Taylor (1984) has given an insightful discussion of this problem and provides guidelines for diagnosis and treatment. In diagnosis, family histories are important because the genetic link provides additional clues to the likelihood that the disorder may be an affective disorder rather than schizophrenia. Furthermore, the diagnosis of schizophrenia on the basis of agitated or bizarre behavior is unreliable, because these behaviors also typify manic disorders. Taylor admonishes clinicians to adhere to an old rule of thumb: When a diagnosis is in doubt and the patient may be suffering from one disease or another, always treat the disease that is easier to cure. In this instance, the affective disorder has the best prognosis. A course of treatment with lithium is very likely to alleviate the manic disorder. If the diagnosis was wrong, treatment with phenothiazines can begin. If the clinician chooses schizophrenia and begins the chronic course of treatment with phenothiazines, the patient is exposed to the high risk of extrapyramidal damage. Taylor points out that schizophrenia is the diagnosis for 4-8% of admissions, whereas the accepted incidence of schizophrenia is about 1-2%; he suggests that permanent brain damage is too high a price to pay for this high rate of misdiagnosis.

E. SUMMARY

Principles

1. The reward system normally functions to energize and direct behavior toward appropriate environmental stimuli. Both norepinephrine and dopamine appear to be involved.

2. Schizophrenia may result from a disturbance of this system, producing the symptomatic changes in

thought patterns, inappropriate affect, and social withdrawal.

3. The consistent rate of occurrence in all cultures and the apparent heritability of schizophrenia strongly suggest a biological basis for the disease.

4. Chlorpromazine and related phenothiazines are powerful antagonists of schizophrenic psychoses.

5. Drugs that are most potent in treating schizophrenia are also the most effective blockers of dopamine receptors. These results suggest that schizophrenia may be the result of excessive dopamine activity.

6. The DBH model suggests that an enzyme deficiency causes dopamine to accumulate and then be transformed into a neurotoxin, 6-hydroxy dopamine. This neurotoxin destroys noradrenergic and dopaminergic terminals.

7. Other theories do not agree with the neurotoxin notion, but nearly all suggest some type of abnormality within the dopamine systems.

8. There is strong evidence that schizophrenic patients have an excess number of dopamine receptors.

9. Chlorpromazine and other drugs that are used to treat schizophrenia typically require several weeks to reach full effectiveness. This suggests that they may act by triggering neuromodulatory processes.

10. Endorphins are likely to be involved as co-transmitters with dopamine and as neuromodulators to change the number or sensitivity of dopamine receptors.

11. The extrapyramidal motor system involves closely related dopamine fibers.

12. Parkinsonism is a movement disorder that involves a deficiency of dopamine receptors, and patients suffering from this disease rarely if ever develop schizophrenia.

13. Drug treatments of schizophrenia often produce Parkinson-like symptoms which may be, in some cases, irreversible.

Terms

6-OHDA

Adenyl cyclase

Amphetamine psychosis

Attention deficit disorder

Autism

Chlorpromazine

Cyclic AMP

D1 and D2 receptors

DBH

Dynamic synapse

Endorphins

Extrapyramidal system

Haloperidol

HVA

Hyperkinesis

Neuromodulation

Nigrostriatal pathway

Parkinsonism

PEA

Phenothiazines

Phosphoinositide cycle

Primary symptoms

Rate limiting enzyme

Reward system

Schizoaffective disorders

Schizophrenia

Second messenger

Tardive dyskinesia

Tyrosine hydroxylase

GENERAL AROUSAL

GENERAL AROUSAL

A. INTRODUCTION

The brain/behavior/environment triangle has been discussed at several points to emphasize the mutual interactions of these three components. It may be useful now to analyze the material that has been covered, as well as the material that is about to be covered, in terms of the way they fit into this interaction. Three general themes can be identified:

- In Chapter 4 and Chapter 5 the primary focus was on the organism's response to adverse environments. These environments led, in turn, to the behavioral and neurochemical changes that we characterized as fear, anxiety, pain, and so on. Various categories of drugs were presented in terms of their ability to ameliorate some of these responses.

- In Chapter 6 and Chapter 7 the primary focus was on pathology of neurological systems. Both depression and schizophrenia were characterized as dysfunctions of the reward system. Various categories of drugs were presented in terms of their ability to restore these aberrant systems back toward the normal condition.

- In the present chapter we will take yet another approach, where both the environmental and neurochemical conditions are within normal and common limits. The organism's level of interaction with the environment fluctuates with its general state of arousal. Various categories of drugs will be presented in terms of their ability to enhance or alter these conditions.

B. SLEEP, AROUSAL AND ENVIRONMENTAL CHANGE

Brain Mechanisms of Arousal

One of the most important developments in the understanding of arousal was Moruzzi and Magoun's (1949) description of the reticular formation of the midbrain (it is called reticular formation because of the net-like anatomical complexity of the small neurons). Damage to this region caused continuous somnolence in the cat, whereas electrical stimulation of the area causes immediate awakening of a sleeping cat. Although the reticular formation receives inputs from the major sensory systems, it does not appear to be a part of the classical sensory projection systems. Based on their experimental observations, Moruzzi and Magoun proposed that the reticular formation was a sort of general "power supply" to determine the level of activity of the entire brain. The functional and anatomical characteristics have been combined in the descriptive term, ascending reticular activating system (ARAS; see Fig. 8.1).

The idea that a brain area was responsible for arousal set the stage for the complementary notions that a brain area could be directly responsible for putting an animal to sleep, i.e., sleep may be an active process rather than a passive result of reduced sensory stimulation. The evidence for this emerged from a number of different experiments that involved transection of the brain at various levels. Transection at the level of the spinal cord had little or no effect on arousal, transection at a somewhat higher level resulted in permanent wakefulness (presumably because of separation from the active sleep centers), and transection at a still higher level led to permanent somnolence (presumably because of separation from centers for arousal). The overall regulation of sleep and wakefulness is complicated, but the diagram in Figure 8.2 is a reasonable shorthand version of these systems.

Sleep and the EEG

On a purely statistical basis, sleep is the most important behavior that we engage in. It normally consumes about a third of our days, and rather steadfastly denies any attempts to significantly change the total amount of or even the pattern of its influence. This has led one sleep researcher (Webb, 1975) to refer to sleep as the gentle tyrant, imposing its demands on our schedules in a most willful manner. But sleep is only one part of a more pervasive tendency of the nervous system to be in oscillation: Whether we are referring to a single cell or to the entire nervous system, there is a cyclic change in activity level, specific biochemical mechanisms to accomplish this change, and an allowance for behavioral modification of the cyclic changes.

It has been known since the early 1800's that electricity was somehow involved in nervous activity (e.g., observations by Helmholtz and by Galvani), but it was not until 1930 that the first electroencephalogram was recorded. Berger (1930) inserted needles just under the scalp (of his son) and was able to record rhythmic electrical waves, the frequency and amplitude of which changed with the level of arousal. This crude demonstration was the beginning of a very active field of study which attempts to use the

electrical activity as a sort of mirror of mental events. The results of these studies have not lived up to the hopes (or in many cases, to the interpretations) of the investigators, with one exception: The EEG has been an indispensable tool in the investigation of sleep and related processes of arousal.

The rule of thumb is that the rhythmic fluctuations of the EEG become slower and larger as the level of arousal declines (refer to Fig. 8.3). It is not necessary for the present discussion to go into the details of the EEG, but there are several important categories that deserve mention. When the eyes are closed and the subject relaxes (without visual imagery), the normally aroused EEG slows to about 10 Hz with an increase in amplitude. This is the so-called alpha wave The alpha state has been touted as a highly desirable state of meditation which can be monitored and fostered by commercial devices costing up to several hundred dollars (alternatively, one can stop looking at the catalogue, close the eyes, and achieve about the same state). If this relaxation continues, the wave slows even more, and the subject enters a rather nebulous state between sleep and wakefulness. This corresponds roughly to the theta wave. The theta state has also been viewed as a desirable state for the creative processes, although the creations are frequently forgotten. Beyond this stage, spiked impulses called sleep spindles appear and the EEG continues to become slower and larger until large, sweeping delta waves are accompanying by the behavioral state of deep sleep.

There is one major exception to the relationship between level of arousal and EEG pattern. Kleitman and one of his students observed periods of apparent deep sleep (arousal was difficult to obtain) during which time the EEG pattern was rapid and small. This so-called paradoxical EEG was accompanied by rapid eye movement (REM) and appears to be related to periods of dreaming (cf., Dement & Kleitman, 1957; Kleitman, 1963).

Most will agree that sleep is a pleasant enough pastime, but it is neither a luxury nor an option. Attempts to eliminate or reduce the amount of sleep are accompanied by compelling urges to sleep. If these urges are fought, irritability ensues and performance becomes impaired. Webb (e.g., 1975) has observed that desert soldiers neglect to keep their canteens filled with water, and nurses fail to make optional rounds to check patients. Eventually, frank psychotic behavior may result, but heroic efforts are usually required to allow sleep deprivation to reach this degree. Webb has remarked that "Sleep is a fixed biological gift and we had better learn to adjust to its requirements rather than try to make it serve our paltry demands." (p. 28 in Goleman, 1982.)

The phenomenon of sleep serves as sort of a caricature for two important observations: (a) cyclic levels of activity appear to be a recurrent theme of brain function, and (b) these differing levels of activity provide different ways of processing environmental information. We turn now to the effects of varying degrees of arousal within the waking state before examining several classes of drugs that have been used to alter, in one way or another, these levels of activity.

The pharmacology of sleep and arousal remains poorly understood. Jouvet (e.g., 1974) has been the

champion of the serotonergic theory of sleep, marshaling considerable evidence that serotonin produced in the raphe nucleus is responsible for the induction of sleep. In general, drugs that inhibit serotonin cause insomnia while the administration of serotonin causes sleep. More recently, sleep onset has been related to benzodiazepine receptors (cf., Chapter 4; Mendelson et al, 1983), but this does not preclude the possibility that these receptors are on cells that release serotonin as the neurotransmitter. On the arousal side, there are at least three candidates for neurotransmitters: dopamine, norepinephrine and acetylcholine. Each of these is released at a higher rate during periods of arousal, and drugs that block the effects of these compounds can produce drowsiness. The general features of these systems is summarized in Figure 8.4. Specific examples will be given later in the chapter.

All of these local changes in sleep patterns and levels of arousal occur against a more global backdrop of circadian (24-hr) rhythms. There is a powerful rhythmicity for virtually all organisms and systems within organisms (e.g., Moore-Ede et al, 1982). Although these rhythms are synchronized with and, in many cases, adjusted by the light/dark cycle, most of these rhythms continue in the absence of normal 24-hr cues. In a dramatic demonstration of this, sleep researcher Nathaniel Kleitman and several associates went deep into a deep cave where they attempted to adapt to an arbitrary 19.5-hr day. None of the individuals could do this; they each showed a so-called "free-running" rhythm that was somewhat greater than 24 hrs, drifting forward with respect to the "real" time set by the sun up at the earth's surface (Kleitman, 1963). The brain area that is responsible for setting many of these circadian events is the suprachiasmatic nucleus, located in the hypothalamus. This nucleus receives information via an accessory optic system (and perhaps through other sensory channels) to adjust and maintain the accuracy of its inherent 24-hr rhythmicity. Injection of radioactive 2-deoxy glucose (2-DG) into brain areas can provide a graphic illustration of the rate of metabolism for a particular area. When this procedure is used to study the suprachiasmatic nucleus, it shows a marked circadian rhythm of activity. This corresponds with fluctuating levels of melatonin that are produced and released by the pineal gland (see Figure 8.5).

Circadian Rhythms

The circadian rhythm is interesting in its own right, but it is especially relevant in the present context because it provides a constantly changing environment in which drugs must act. Changes in hormone levels, body temperature, rate of metabolism, heart rate, blood pressure, gastrointestinal activity, sleep cycles and behavioral activity levels all change markedly on a 24-hr schedule. A drug that interacts with any of these (and how could one not!) will have differing effects for a given dosage, depending upon the time of day. This can be shown dramatically in the case of anesthetic drugs, which are effective in much lower dosages during the rats' normal (daytime) quiet periods (Davis, 1962; see Figure 8.6). Higher doses are required during the active periods, increasing the risk of overdose (Pauly & Scheving, 1964). Conversely, drugs that specifically alter any of these physiological systems have the potential to disrupt the normal rhythmicity and cause secondary problems.

Arousal as Reward

The level of arousal on a more local or moment to moment basis has been linked closely to the phenomena of motivation and reward. One of the earliest and most influential statements about this relationship is the Yerkes-Dodsen Law (1908) which states that an organism interacts most efficiently with its environment when the level of stimulation is at some intermediate level; below this level the arousal level is too low and the organism misses essential features of the environment, while levels of arousal that are above the optimal result in exaggerated responses to all elements and a decrement in performance. As shown in Figure 8.7, this relationship between arousal and performance can be characterized as an inverted U-shaped curve.

The importance of this formulation is not just that behavior changes when the level of arousal changes, but that behavior is also an important way to achieve a change in arousal. Butler (1958), for example, found that monkeys would press a lever in order to open a small window that would allow them to see the laboratory or hear the sounds of the monkey colony. Similarly, Tapp (1969) showed that rats will press a lever to turn on a light for a brief period. These exploratory behaviors, as well as several different types of locomotor activity (e.g., running wheel, tilt cages, jiggle cages, open field, etc.) are all behaviors that cannot be explained by the traditional motivators of hunger, thirst, or reproduction. Rather, these behaviors appear to be reinforced simply by the feedback from the responses. Interestingly, a rat will run considerably more if it has a food pellet in the running wheel. Not because it wants to eat it, but because it makes more noise! A marble works as well.

The idea that a rat or monkey would perform a response out of "curiosity" or an "exploratory drive", with the result being nothing more than a change in arousal level was a bold proposal. It flew in the face of the very thorough and formal drive theory of Hull (1952) and Spence (1956.) But even traditional drive theory assumes an important role for arousal. The drive state is said to have two effects: (a) an energizing effect that increases the general behavior of the organism, and (b) a directing effect that channels the behavior toward relevant goal objects. When reinforcement is obtained, the drive and its resulting energy is reduced. When extinction or nonreinforcement in encountered, the energy is intensified and the behavior is less channeled.

In summary, the brain systems that control arousal are subject to the same controls and interactions that we have seen for other behaviors (cf., Fig. 8.8). The environment can adjust or change the level of arousal, which results in changes in behavior. But changes in behavior also produce changes in the level of arousal, and behaviors may occur for the purpose of changing arousal levels. Furthermore, the behavior can actually change the environment, or at least move the organism to a different part of the environment. Finally, drugs can rather directly enter into this scheme by changing the level of arousal. It should not be surprising, therefore, that these drugs have assumed considerable importance both in the practice of medicine and as a part of human cultures. Because of their action on the very core of behavior, these drugs are often overused or abused, having social consequences that may outweigh their effects on an individual. We turn now to a discussion of some of the pharmacological and behavioral effects of these drugs.

C. DRUGS THAT INCREASE AROUSAL

Strychnine, Picrotoxin and Pentylenetetrazol

The complexities of behavioral arousal (e.g., involvement of several different neurotransmitters, interaction with the reward system, etc.) provides many different points at which drugs may influence the system. The three drugs that are considered in this section are representative of a class of drugs that have rather general excitatory effects through their actions on inhibitory neurons or directly on the properties of the action potential (see Franz, 1980 for a detailed treatment).

Strychnine is an extremely potent drug that causes general excitation of the central nervous system, especially the reflexes of the spinal cord. This bitter tasting substance is derived from an extract of a tree that is native to India. It has a long history of medicinal use, as a general tonic, to increase the appetite, to cure constipation, and as a general stimulant. Commercial forms of the substance were once widely available as so-called "bitters" and can still be obtained in some over-the-counter preparations. There is virtually no evidence that strychnine has any general curative properties, and it is a very dangerous drug to use as a stimulant.

Strychnine has also been used (probably inappropriately) in more traditional medicine as an antidote for the respiratory and cardiovascular depression that occurs with barbiturate or anesthetic poisoning. Again, there is probably no rational basis for this, since the addition of the second drug only complicates the already challenged physiology of the patient. It is usually more advisable to use mechanical means of supporting the respiratory and cardiovascular deficiencies of the patient.

Currently, strychnine is used in some street formulations to add a stimulating effect to a variety of different drugs. It is especially dangerous in this informal context, because of potentially lethal overdoses or interactions with other drugs.

Strychnine has played an important role in research as a tool to help unravel some of the mechanisms of brain and spinal cord circuits. High dosages of strychnine produce an exaggeration of spinal reflexes that can result in tonic seizures with the limbs rigidly extended (an interesting exception to this is the sloth, which shows extreme flexion owing to the reversed organization of its anti-gravity muscles.) The most likely action of strychnine is that it excites these actions by blocking the normal inhibitory effects (see Figure 8.9).

The Renshaw cell, an interneuron of the spinal cord, has long been of interest because of its receptors. It was known that the alpha motor neurons release acetylcholine at the nerve-muscle junction. Because of Dale's law (which may still be in effect in this instance) that any neuron manufactures and releases only one neurotransmitter, the Renshaw cell was the first neuron within the central nervous system that was known to be cholinoceptive. The transmitter substance released by the Renshaw cell was not so easily determined, but electrophysiological studies revealed that it had an inhibitory effect on the alpha motor

neuron. More recent investigations indicate that glycine is the transmitter substance, and both glycine and strychnine bind to the same receptor sites on the alpha motor neuron. Thus, it would appear that strychnine stimulates activity in spinal reflexes by blockade of the recurrent inhibition produced by the Renshaw cells. Tetanus toxin, which causes similar convulsive activity, does so by blocking the release of the transmitter, rather than blocking the receptor sites.

Another naturally occurring substance, picrotoxin, is derived from the seeds of the fishberry shrub (so named because the berries were fed to fish so they would float to the surface). This drug also stimulates nervous system activity by blocking inhibition, but apparently through different mechanisms than strychnine. It appears to block the receptors that normally mediate the inhibitory effects of GABA (see Figure 8.10); GABA refers to gamma amino butyric acid. In fact, most of the evidence for GABA as a central neurotransmitter is based upon the experimental effects of picrotoxin.

A third compound that has been widely used for research purposes is a synthetic drug called pentylenetetrazol (Metrazol). It appears that this drug does not interfere with any particular transmitter, but rather reduces the recovery time following action potentials. As indicated in Figure 8.11, this is probably accomplished by increasing the permeability to potassium, leaving the cell in a state of partial depolarization. Pentylenetetrazol has been used as a seizure inducing drug in the process of screening drugs that may have anticonvulsant activities.

The Xanthine Derivatives

The xanthine derivatives are by far the most widely used stimulants, and appear to be safe in moderate dosages (see Rall, 1980 for a review). The most common and most potent of these is caffeine, with theophylline being somewhat less effective, and theobromine being considerably less effective. All three substances are present to varying degrees in coffee, tea, cocoa and cola (see Table 8.1):

TABLE 8-1

Annual Consumption of Xanthine Derivatives		Relative Caffeine Content	
Coffee	10 pounds	1 cup coffee	2 cups tea
Cocoa	3 pounds	1 cup coffee	24 oz cola
Tea	1 pound	1 cup coffee	20 cups cocoa
		1 cup coffee	5 oz chocolate

(Cocoa contains much more theobromine.)

As in the case of pentylene tetrazol, these compounds have not been linked to a specific transmitter. They appear to cause an increase in calcium permeability, and may increase cyclic AMP production (see Fig. 8.12). These actions stimulate a wide range of physiological systems and mood changes. The major psychological effects include a decrease in fatigue and drowsiness, an increase in speed and efficiency, and a decrease in the number of errors (especially in an over-learned task such as typing). They increase the ability to do muscular work, including an increase in the action of the heart muscle. Peripheral vasodilation increases the perfusion of organs (including the diuretic effect on the kidneys), except for the brain, which shows a decrease in blood flow. This latter effect may account for the fact that coffee is effective in relieving hypertensive headaches for some individuals. The increased gastric acid secretion can be a liability, especially for those who may be prone to the development of gastric ulcers, but this effect appears to be blocked completely by cimetidine (see Chapter 6). In general, these compounds provide safe stimulating effects that do not appear to lead to serious abuse.

Nicotine

Nicotine is a powerful stimulant that is most commonly administered by smoking tobacco. It was in widespread use throughout the Americas when the first European explorers arrived. Tobacco use (chewing, smoking, and snuffing) has had many stormy periods in terms of cultural and legal acceptance (and is in another right now), but for the most part, the use of tobacco has prevailed (cf., Ray, 1978). In 1978, more than a decade after the Surgeon General's cancer warning, about 4,000 cigarettes were sold for every person over 18 in the United States. The health hazards are legion, but for the present purposes we shall consider only those that relate to the direct neuropharmacological effects and ignore the potentially more threatening effects of the associated tars and additives.

Nicotine produces a bewildering array of influences, most of which occur by virtue of its ability to *mimic* acetylcholine at certain receptor cites (e.g., Taylor, 1980). In fact, the categories of acetylcholine receptors (muscarinic and nicotinic) are defined, in part, by their responsiveness to nicotine (cf., Chapter 1). In the periphery, nicotine acts on the autonomic ganglia. This action is complicated not only because it acts on both sympathetic and parasympathetic ganglia, but also because of the *biphasic action* of the compound. At low dosages or during the initial stages of higher dosages, the effect is one of stimulation, and expected changes in autonomic effector cells can be observed. But unlike acetylcholine, nicotine is not rapidly inactivated by acetylcholinesterase, and its long lasting effects on the receptors lead to prolonged depolarization. This paralysis of ganglionic activity occurs not only while the cells are depolarized, but appears to continue for some time after normal polarization has been restored. At moderate dosages, some ganglia may be more affected than others, so heart rate (for example) could be increased either by stimulation of sympathetic ganglia or by paralysis of the parasympathetic inhibitory effects. Contrariwise, heart rate could be decreased by relative stimulation of the parasympathetic or paralysis of the sympathetic ganglia. Some of these increases may be dangerous, because the oxygen demands of the heart muscle may be increased while the oxygen supply remains the same. This could

trigger cardiac failure in certain individuals. Figure 8.13 summarizes the synaptic effects that mediate these physiological changes.

Nicotine also acts on skeletal muscle receptors, but the initial stimulation phase is either very short lived or nonexistent. The overall effect is, therefore, a relaxation of these muscles at low or moderate dosages and paralysis at higher dosages.

Nicotine also influences neurons throughout the central nervous system, although the distribution of these remains rather ill-defined. The drug appears to produce its central effects through both a direct action on cholinoceptive cells, and indirectly through stimulation of dopaminergic fibers. The administration of nicotine produces a rapid arousal of the EEG and an increase in the release of norepinephrine and dopamine. Although the implications are not clear, it also increases the release of growth hormone, antidiuretic hormone, and cortisol. Acute nicotinic poisoning can lead to nausea, vomiting, diarrhea, and ultimately respiratory and cardiovascular collapse. In lower dosages, the untoward gastrointestinal symptoms rather quickly disappear through tolerance, but the EEG arousal effects continue. Although the mechanisms are not yet known, it appears that the chronic administration of nicotine can lead to enzyme induction which facilitates not only the metabolism of nicotine, but other apparently unrelated stimulants such as the xanthine derivatives and various drugs that act on the catecholamine systems.

Sympathomimetics

The sympathomimetic compounds mimic or otherwise increase the activity of neurotransmitters associated with the sympathetic nervous system, namely, norepinephrine and dopamine(cf., Weiner, 1980b). The most widely used drugs within this class include the amphetamines and cocaine. Although the mechanisms of action of these drugs differ, they act upon the same neural substrates, and their effects upon mood and other behaviors are remarkably similar. These drugs are powerful stimulants of the central nervous system, and in moderate dosages, they produce EEG and behavioral arousal, decreased fatigue and boredom, increased psychomotor performance, decreased appetite, and elevations in mood that are frequently described as euphoria. At higher dosages they produce a variety of motor symptoms (twitching, restlessness, stereotyped repetition), perceptual symptoms (distortion of time, tactile hallucinations or the so-called "cocaine bugs"), mood distortions (fear, paranoia, psychotic symptoms), and the possibility of convulsions and death.

Amphetamines

The amphetamines have a variety of different effects on neurons that release catecholamines, including the ability to directly mimic the neurotransmitters at the receptor site. Their major action, however, appears to be the indirect release of newly synthesized dopamine (and perhaps norepinephrine); if the enzyme of synthesis, tyrosine hydroxylase, is inhibited, the effect of amphetamine is greatly reduced (see Fig. 8.14).

The long term effects of the amphetamines may include some serious dangers to the motor system. The symptoms include an increase in the startle response, twitching, and related dyskinesias that may be due to a reduction of dopamine in the caudate. The most likely cause of this decrease is a chronic decline in tyrosine hydroxylase activity, which is probably attributable to erroneous feedback from the increased transmitter release.

Cocaine

Cocaine is present in the leaves of a shrub that grows high (so to speak) in the Andean mountains of South America. The natives have chewed or sucked on these leaves for centuries (averaging as much as four or five kilograms of leaves per year) for the elevation of mood that is produced. It also produces a numbing sensation because of its local anesthetic actions, but was not used clinically as a local anesthetic until Sigmund Freud made this suggestion. In the early 1900's synthetic substitutes (e.g., procaine, lidocaine, xylocaine) began to be produced, but none is as effective as cocaine in blocking pain, although all appear to have some euphoria producing effects. Cocaine is still widely used and abused as a street drug, and also continues to be used clinically because of its unparalleled strength and duration of local anesthesia for eye, nose and throat surgery.

Cocaine acts on the same neuronal systems as amphetamine, but enhances the effects of catecholamines (primarily dopamine) by blocking reuptake (see Fig. 8.15) rather than stimulating release (Ritz et al, 1987).

The local anesthetic properties of cocaine and the synthetic derivatives appear to be the result of direct actions on the cell membrane. These changes block the transient change in sodium permeability that is necessary for the propagation of the action potential. This action continues as long as the drug is in contact with the cell, so most preparations include a solution of epinephrine and norepinephrine to produce vasoconstriction that prevents the dispersion of the drug. One of the reasons that cocaine is so effective is that it serves as its own vasoconstrictor through its action on local sympathetic terminals.

The powerful behavioral effects of cocaine and the amphetamines are probably due to their effects on two populations of brain cells. One effect is to increase the general level of arousal by stimulating the catecholamine containing neurons that are involved in this system. The other is to stimulate the catecholamine containing neurons that are involved in rewarded behavior. Together, these effects are very potent: The organism is more responsive to the environment, and the rewarding effects of that environment are amplified.

D. DRUGS THAT DECREASE AROUSAL

Benzodiazepines and Barbiturates

The hypnotic and sedative drugs were discussed in Chapter 4 in terms of their rather specific abilities to

counter fear and anxiety. They have also been used extensively in the clinic for their related abilities to promote sleep and, in high dosages, to produce varying degrees of anesthesia. The general effects of these drugs include a shift toward slower EEG frequencies (indicating lowered arousal), a decline in psychomotor performance, and reduced perceptual abilities. Although they promote sleep, there is frequently a reduction in the important REM stage of sleep.

Both the benzodiazepines and the barbiturates reduce the activity of excitable tissues, but their effects are much more pronounced on the central nervous system. Their action is widespread, but appears to selectively influence polysynaptic pathways that involve small fibers (most notably, cortical functions and the reticular formation). As indicated in Figure 8.16, these drugs apparently lower arousal by virtue of their interaction with neurons that release the inhibitory transmitter, GABA. This neurotransmitter is apparently involved with both presynaptic and postsynaptic inhibition of a variety of different transmitters, but certainly includes those transmitters that are involved with arousal systems. (Note that these effects are directly opposite those produced by picrotoxin, cf., Figure 8.10).

In discussing the effects of the benzodiazepines, it was noted that these compounds bind rather specifically to receptor sites in the brain that do not appear to be involved with any known neurotransmitters. The conclusion was that there may be endogenous benzodiazepines which are involved in counteracting anxiety. Extending this model into the present context, it might be proposed that the GABA releasing neurons have receptors that are specific for the benzodiazepines. Further support for this indirect action is the observation that depletion of GABA prevents the sedative effects of the benzodiazepines.

Figure 8-16 summarizes the current model of the GABA receptor complex. This receptor complex appears to have three separate, but interacting receptor sites: a sedative/hypnotic site, a benzodiazepine site, and a GABA site. The inhibitory effects of the GABA neurotransmitter appear to be mediated by the enlargement of the chloride (Cl-) channel. This effect is augmented by the presence of either barbiturates or benzodiazepines, and blocked by convulsants.

One of the difficulties with the model shown in Figure 8-16, is that the benzodiazepines and barbiturates have been classified as different types of drugs on the basis of their differing clinical effects. In particular, the benzodiazepines are more effective in the reduction of anxiety, while the barbiturates are much more effective as general anesthetics. One possibility is that these compounds share the ability to enhance the activity of GABA, but that the barbiturates are less specific in this regard and have additional effects as well. In particular, there has been evidence that the barbiturates may block the reuptake of GABA and may be specifically involved in blocking the activity of certain synapses that utilize norepinephrine or acetylcholine. The barbiturates seem to produce a slower recovery time of neurons, which is of little importance in a single synapse, but produces substantial impairment in pathways that involve multiple synapses.

Both the barbiturates and the benzodiazepines have been used to treat sleep disorders, but with mixed results. These drugs make it easier to fall asleep, and may increase the total time spent sleeping, but in

many cases there is a reduction in the amount of REM sleep. As a result, the sleep is less effective than normal and the patient becomes more sleep deprived. Dement (1974) and other sleep researchers have cautioned against the use of so-called sleeping pills, because many of them are more likely to cause insomnia than to cure it!

There is some evidence that the benzodiazepines may be useful in preventing the disruptive effects of changing one's circadian rhythms (e.g., with shift work). Seidel and associates (1984) imposed an abrupt 12-hr shift in the sleeping schedule of volunteers, delaying their bedtime from midnight until noon. Over the course of the next three days, untreated subjects experienced a loss of sleep and impaired function during the waking hours. Subjects treated with triazolam, a fast acting benzodiazepine, did not show these disruptive effects.

Alcohol

Alcohol is one of the most ancient of drugs, with references to its use appearing in some of the earliest recorded histories (cf., Ritchie, 1980). Alcohol use and abuse probably even preceded the appearance of the human species, since it has been shown that a variety of animals (e.g, birds, bees, wild pigs, and even elephants) have been known to partake of the naturally fermenting fruits. The fermentation process can produce concentrations of ethyl alcohol in the range of 12 to 14 percent, at which point the reaction is self limiting because the alcohol kills the yeast that supports the fermentation process. This limits the concentration of naturally fermented wines and beers (mostly 4% in the United States). However, man was quick to increase the potential of this drug, and the Arabs invented the distillation process some 1200 years ago to extract higher concentrations of alcohol. This alcohol can be produced from a variety of different sources, including fruits, grains, and even potatoes. Almost every known culture has contributed to the science and the business of producing alcohol, and we now have a staggering array of "preparations" of this compound from which to choose.

The mechanism of action of alcohol remained a mystery for many years despite the intense research efforts that were aimed toward a better understanding of this drug. It is certainly a local irritant, which can lead to the inflammation of tissues, especially the membranes. In sufficiently high concentrations, it can even serve to coagulate protoplasm and kill the cells. These effects on cell membranes can reduce the ability of peripheral nerves to conduct impulses (by decreasing the permeability to both sodium and potassium), giving alcohol some local anesthetic properties.

All of the effects noted above occur in concentrations that are many times greater than the plasma concentrations that are reached in the blood. As in the case of the benzodiazepines and barbiturates, alcohol appears to selectively influence polysynaptic pathways, in part at least, through the facilitation of GABA. Although the details of the interaction are not yet fully known, alcohol can be very dangerous when taken in combination with a sedative compound such as Librium or Valium. Normally safe dosages of each compound can combine synergistically to produce coma or death.

The behavioral effects of alcohol are comparable in many respects to those produced by the

benzodiazepines and barbiturates. As shown in Figure 8.17, there is a selective depression of the reticular activating system and a corresponding increase in EEG slow wave activity. Inhibitory processes decline first and with smaller dosages, resulting in an exaggeration of spinal reflexes and the appearances of behaviors (e.g., talkative, boisterous, aggressive, etc.) that are normally under the influence of social inhibition. Hence, the mistaken notion that alcohol is a stimulant. These effects precede or are accompanied by a marked decline in perceptual abilities (especially pain) and psychomotor functions (especially previously trained responses). There is virtually no evidence that alcohol can enhance motor or cognitive abilities beyond normal, except in those cases where some aspect of the behavior is inhibited (e.g., it would probably greatly enhance the ability to swim in the nude at one's in-laws). At very high dosages, alcohol has general anesthetic effects, but it is not medically useful in this regard because the anesthetic dosage is very close to the lethal dosage. In this regard, it should be pointed out that alcohol is a dangerous drug strictly on the basis of its therapeutic ratio. Suppose, for example, that one considers two or three drinks to be the effective dose for the "desired" effects of alcohol. A dosage of 12 to 15 drinks represents a dangerous overdose that can lead to coma or death. This yields a therapeutic index (LD/ED) in the range of about 6, which is much too low to be considered safe. It is for this reason that hazing rituals, drinking contests, and so forth so frequently result in tragic death.

The behavioral effects of alcohol are accompanied by a variety of physiological changes which, interestingly, fall into a pattern that is very much like that of a general *stress* response. The local irritating effects on the oral membranes, gastrointestinal tract, and somatic muscles trigger histaminic reactions. There is an increase in the release of ACTH and adrenal hormones. Lactic acid and fatty acids are released into the bloodstream, the heart rate increases, and peripheral vasodilation occurs. There is a decrease in antidiuretic hormone that increases urine outflow which can result in the depletion of calcium, magnesium and zinc. These responses form an important part of the general abuse syndrome, which will be discussed later in this chapter.

The behavioral and physiological effects of alcohol are closely related to the concentrations of the drug that appear in the bloodstream. This is true for nearly all drugs (cf., Chapter 3), but has assumed greater significance in the case of alcohol because the plasma level has become almost synonymous (legally synonymous in many states) with the level of intoxication. There is a germ of truth in some of the folklore concerning the effects of alcohol. Absorption is slower in the stomach than in the intestine, so anything that helps to retard the progress of alcohol from the stomach into the small intestine will also retard the climb in blood alcohol levels. Fatty foods, milk, and meat all cause reflexive closing of the stomach valves to allow greater digestion at this stage, and indirectly result in slower absorption of the alcohol. Meanwhile, the liver enzymes are breaking down the alcohol as it enters the bloodstream, so the overall effect of a particular dosage of alcohol will be prolonged, but the peak effect will be lower. Carbonated beverages enhance the absorption process, highly concentrated drinks slow down absorption, and emotional changes can either increase or decrease absorption. Finally, the effectiveness of a given blood level of alcohol is greater on the ascending side of the curve than on the descending (especially when the rate of ascent is rapid), presumably because some of the cells of the nervous system become somewhat refractory to the alcoholic environment and resume some of their normal functions before the blood alcohol concentrations begin to decline.

Regardless of these influences on absorption rates and other aspects of blood alcohol levels, the alcohol is ultimately metabolized to produce energy. The first stage of this reaction converts the ethyl alcohol into acetaldehyde. The acetaldehyde is poisonous, but the presence of the enzyme acetaldehyde dehydrogenase normally results in the quick conversion of this compound into acetic acid. The drug known as Antabuse (disulfiram) interferes with this enzyme and allows the acetaldehyde levels to build up and cause illness following alcohol ingestion. Genetic variations in this enzyme system may contribute to individual differences in the tendency to consume alcohol (cf., Horowitz & Whitney, 1975).

Anticholinergic Drugs

The involvement of acetylcholine in arousal suggests that the anticholinergic compounds might provide a powerful method of lowering arousal levels. The cholinergic blocking drugs such as atropine and scopolamine compete with acetylcholine at muscarinic synapses throughout the nervous system and especially in certain parts of the limbic system (see Fig. 8.18). When these compounds were discussed for their potential antianxiety effects (cf., Chapter 4), it was noted that one of the major drawbacks was that the compounds were too broad in their spectrum of action. Their action within the parasympathetic system produces such undesirable side effects as dry mouth, pupil dilation with blurred vision, rapid heart beat with palpitations, and others. These same disadvantages apply to the potential use of these drugs for their hypnotic or sedative effects. It is interesting, in this regard, that these compounds seem to have only modest potential for abuse, despite their very real effects on the central nervous system.

Although atropine and scopolamine are not used routinely for their sedative effects (except as a presurgical treatment), they have been important as a research tool. The effects of cholinergic blockade have been used as an example of those uncommon situations in which the EEG seems to be dissociated from behavior. Rinaldi and Himwich (1955) reported that atropine produces a slow-wave EEG that is typical of sleep, but that the animal was still behaviorally awake. A more accurate portrayal of this paradox might be that the animals show a slow-wave EEG while not being behaviorally asleep--their state of wakefulness is somewhat questionable. High dosages of cholinergic blocking agents greatly reduce the activity of rats in their home cage, and although they appear to be awake (eyes open, upright), there also appears to be a lack of "voluntary" attention to the environment (not unlike the state of college students during lectures). Yet, these rats will show a greatly enhanced response when given the opportunity to explore a new environment or when presented with specific external stimuli such as loud noises.

The effects of these drugs have been linked to the action of the septohippocampal system (cf., related discussion of behavioral inhibition in Chapters 1 & 4). It appears that the septum contains cholinoceptive neurons that project to the hippocampus, producing the characteristic theta pattern in the hippocampal EEG. This hippocampal theta activity is seen in a variety of situations that involve attention to new aspects of the environment or to changes in the rewarding contingencies of the

environment (most notably, nonreinforcement or punishment). The blockade of this system with cholinergic blocking agents results in a variety of deficits that can be characterized as disinhibitory or failures of attention (see Gray, 1970).

E. DRUGS THAT CHANGE PERCEPTION

There is probably no other area of behavioral pharmacology that has so rich a mine of interesting stories. There is, for example, the often quoted drug experience of Hoffman's discovery of LSD, or one of the many stories of pagan (and not so pagan) rituals that involve the drinking of urine to obtain the non-metabolized drug that passed through the first user's body, or a description of colonial soldiers gamboling about under the influence of scopolamine. It is tempting to expand these anecdotes, but the bottom line is that a good pharmacological story cannot be related--there is no specific mechanism of action or neurotransmitter interaction that can account for the effects of these drugs. There are, however, some general considerations about the behavioral changes that should be discussed.

The drugs that alter perception have been somewhat loosely classified on the basis of their ability to produce distorted experiences of the environment. Descriptions of these effects allude to dreamlike states, orgasmic feelings, florid visual imagery, a sort of distortion of time and space, synesthesia (hearing visual stimuli, seeing odors, etc.), a feeling of oneness with the universe, a feeling of separation from the universe, and so on. These experiences, which seldom occur with other drugs or in the absence of drugs, have led to the terms hallucinogenic, psychedelic, psychotomimetic, mind altering, or even mind expanding drugs.

A logical case can be made that all centrally active drugs alter perception. For example, the stimulant and depressant drugs that were just discussed can produce changes in mood and level of arousal. Since an individual's interpretation of the environment is heavily dependent on mood and arousal, changes in perception certainly will occur. In fact, one of the major reasons for the voluntary consumption of drugs like alcohol may be to reduce the perception of anxiety provoking stimuli in the environment. (This is not to say which, if either, set of perceptions is veridical; initially false perceptions fall prey to drug effects as easily as those that can be verified.)

In defense of a special category for the hallucinogenic drugs, the altered perceptions produced by most other classes of drugs are much less profound. This does not mean that the drugs, as a class, share a common mechanism. Their actions are diverse: Scopolamine and related compounds block the cholinergic receptors, LSD and related compounds are serotonergic agonists, the amphetamines and cocaine stimulate systems that use norepinephrine and dopamine, the recently infamous phenylcyclidine (a.k.a. PCP, PeaCe Pill, angel dust, Hog) influences several different transmitter systems, while the specific actions of the much studied marijuana remain unknown. Any attempts to build an all encompassing theory forces one into complex notions such as the balance among transmitter systems and the unsatisfying conclusion (already made) that any drug would be expected to alter perceptions.

The lack of a common biochemical action is not the only problem encountered in the study of this class

of drugs. The behavioral effects have been equally difficult to study. Animal models seem rather silly when one is talking about hallucinations, artistic creativity or oneness with the universe. Nonetheless, there have been reports of monkeys grasping for apparently hallucinated objects in empty space (at least it appeared empty to the investigators), of cats stalking unobservable prey, and of spiders spinning unorthodox webs. This is not to say that animals do not experience and perhaps even appreciate the effects of mind altering drugs, but simply that the effects that are being championed by the users of these drugs are too close to the human experience to make an animal model very useful. But the problem is not solved by turning to human studies. Objective measures of performance (even creativity and imagery) can be obtained, but many of the changes must rely on subjective reports, and when the drug is effective, these reports must be obtained from an individual who has an altered interpretation of the environment.

The widespread use of drugs for the purpose of altering perception has led to an unwarranted mystique about the properties of these drugs. A recurrent theme in the description of the drug states is that the experience is unparalleled in the normal condition, except for dream states, hypnotic or meditative trances, and religious rapture. While this is probably true, it should serve to diminish rather than elevate the uniqueness of the drug effects. Hypnotic trances, for example, have been viewed as something of the occult, with both the mind and the body under the direct control of the hypnotist. Careful, objective studies reach less dramatic conclusions, and have shown that the so-called trance includes the full range of normal EEG arousal and that the "feats" of rigidity, induced sensory impairment, and even blister formation are all within the boundaries of phenomena that can be done on command by many non-hypnotized individuals or by individuals pretending to be hypnotized (cf., Dalal & Barber, 1972; Orne, 1979).

The normal non-drugged state may also be overrated in terms of its ability to provide a constant and accurate view of the world. Illusions abound. One need only to lie down beside a church and gaze skyward to see the tall spire apparently falling continuously as the clouds sweep by. If one were to nurture this illusion in the same fashion as a drug induced effect, it might well turn into a religious experience.

The misconception of all of these phenomena is that there is something inherent in the drug or hypnotic induction that introduces these experiences. But it is not like bringing in a motion picture reel from some mysterious external source. To borrow and paraphrase an old adage about computer data processing, "crap in; crap out", the brain has only its own information to work on. Altered states of consciousness induced by hypnosis, meditation, drugs, or sleep can do nothing more than rearrange or reinterpret past experiences in the context of the ongoing environment. In the normal, alert waking state, our nervous systems have a long history of selection that has favored a slightly distorted (rocks really do fall faster than feathers) Newtonian interpretation of the universe. The simplest conclusion from all of this appears to be the unsatisfying one that we described earlier: The disruption of any of the major systems that are involved in arousal (ACh, 5-HT, NE and DA) can alter these perceptions in strange and sometimes rewarding fashion.

F. SUMMARY

Principles

1. The daily, cyclic activity of the brain is accompanied by changes in mood, arousal, and a variety of physiological changes.

2. The EEG continues to be active during the daily periods of sleep. This EEG is characterized by 90-min cycles that coincide with periods of REM and dream reports.

3. The ascending reticular activating system is an important brain structure for the maintenance of arousal.

4. Dopamine, norepinephrine and acetylcholine have all been related to arousal; serotonin has been related to sleep.

5. Drug effects change dramatically as a function of the background level of arousal at the time of administration.

6. Strychnine, picrotoxin and pentylenetetrazol produce CNS stimulation by blocking inhibition or reducing recovery time between action potentials.

7. The xanthine derivatives increase arousal by increasing calcium permeability.

8. Nicotine mimics acetylcholine and produces arousal by acting on CNS neurons as well as stimulation of autonomic ganglia.

9. Cocaine and amphetamines are sympathomimetic and increase arousal and the effects of reward.

10. Cocaine and related local anesthetics block sodium channels and interfere with the propagation of action potentials.

11. The hypnotic and sedative drugs reduce arousal and may induce sleep, but they may also interfere with REM sleep. They probably act by facilitating the action of GABA.

12. Alcohol produces many of its effects by acting on the same polysynaptic systems that are influenced by the sedative and hypnotic drugs, probably through the GABA receptor complex.

13. Anticholinergic drugs reduce arousal levels, but also interfere with behavioral inhibition and attention.

14. Hallucinogenic drugs do not seem to fall into a class in terms of the cell population or neurotransmitters that are affected.

Terms

2-deoxy glucose

Acetaldehyde

Acetaldehyde dehydrogenase

Alcohol

Alpha waves

Amphetamine

Anticholinergic

ARAS

Atropine

Barbiturate

Benzodiazepine

Ca^{++} channels

Caffeine

Cholinomimetic

Circadian rhythm

Cl- channels

Cocaine

Delta waves

Disulfiram

GABA

GABA receptor complex

Ganglionic stimulation

Glycine

Hippocampal theta

LSD

Melatonin

Na^+ channels

Nicotine

Pentylene tetrazol

Phenylcyclidine

Picrotoxin

Pineal gland

Postsynaptic inhibition

Presynaptic inhibition

Raphe nucleus

REM sleep

Renshaw cell

Reticular formation

Scopolamine

Serotonin

Suprachiasmatic nucleus

Sympathomimetic

Tetanus toxin

Theobromine

Theophylline

Theta waves

Tyrosine hydroxylase

Xanthines

Yerkes-Dodsen Law

TOLERANCE, DRUG ABUSE AND HABITUAL BEHAVIORS

A. MECHANISMS OF TOLERANCE

General Features

Tachyphylaxis

Changes in Receptor Sensitivity

Enzyme Induction

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B. BEHAVIORAL CONTRIBUTIONS

Behavioral Tolerance

Pre-Post design.

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C. FOUNDATIONS OF ABUSE

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D. SUMMARY

Principles

Terms

TOLERANCE, DRUG ABUSE AND HABITUAL BEHAVIORS

A. MECHANISMS OF TOLERANCE

General Features

The introduction of a drug into a biological system is far more complicated than adding a compound into a test tube. The initial dosage of the drug, the route of administration, the rate of absorption, the rate of elimination and many other factors enter into this complex equation. Ultimately, the effectiveness of the drug is usually determined by the concentration of drug molecules in the plasma that are free to interact with receptor sites (cf., Chapter 3).

The distribution of drug molecules to the receptor sites may be complicated, but it is only the tip of the iceberg in terms of the organism's overall response to the drug. Early in the text, a somewhat loose distinction was made between a drug action (how the drug interacts with a specific receptor, e.g., mimicking acetylcholine at muscarinic receptors) and a drug effect (the physiological or behavioral results of this drug action; e.g., a decrease in heart rate or an increase in arousal level). There is yet another class of drug effects that may or may not involve the specific receptors that mediate the drug action: The presence of the drug may trigger any of several different responses that change the reaction to future encounters with the drug. This altered response to the drug is usually a decrease (tolerance), although increased response to the drug (sensitization) can also occur.

The body has two general methods of increasing its tolerance to a drug. One of these is to reduce the opportunity of the drug to reach the receptors (i.e., reduce the drug action), the other is to launch a biological counterattack against the drug effect (i.e., a compensatory reaction).

There are several different ways in which the receptors can be insulated from the drug. The entry of free drug molecules into the bloodstream can be reduced by lowering the rate of absorption from the stomach and intestines. This might be accomplished mechanically by a change in blood flow or peristaltic action, or biochemically by a reduction of the transport mechanisms that may be required to carry the drug molecules across the membranes and into the plasma compartment. Another possibility is to allow the drug to enter the bloodstream in exactly the same way, but to reduce the final level that is reached by increasing the rate at which the drug is eliminated (e.g., by the kidneys or liver). Finally, it may be possible to increase the binding of drug molecules into complexes with other, larger molecules to render them inert. Figure 9.1 summarizes these mechanisms of tolerance.

There are also several alternatives through which a compensatory response can be made to drug effects. One of the most straightforward ways is to increase the activity of an opposing system. For example, if a sympathetic agonist is increasing the heart rate, this could be countered by an increase in parasympathetic activity that reduces the heart rate. Although the contrapuntal relationship between the sympathetic and parasympathetic systems has been overrated, mutual feedback systems do tend to modulate and balance the activity of these systems, and some brain systems may have comparable patterns of organization. The details of this compensatory response are usually not clear for any individual case, but the general features probably involve neuromodulation, which has already been discussed in other contexts. If, for example, a drug reduces the amount of transmitter that is released, the postsynaptic cells may respond by increasing the number and or sensitivity of receptor sites to maximize the effect of the available transmitter molecules. (This process is basically the same as denervation supersensitivity, a phenomenon which can occur if the fibers coming into a cellular region have been cut and allowed to degenerate. Following the degeneration, the cells that have lost their inputs frequently show an increase in the number of receptor sites and become supersensitive to even small amounts of the missing transmitter substance.) Alternatively, agonists may cause the postsynaptic cells to reduce the number of receptors to prevent excessive levels of stimulation. At a still more complicated level, behavioral tolerance may enter into the picture, with the organism learning or otherwise adapting to the effects of the drug, such that the behavior is normalized in spite of any prevailing physiological changes that the drug may produce. These compensatory mechanisms are summarized in Figure 9.2 (cf., Ellison et al, 1978; Lee & Javitz, 1983; Schwartz & Keller, 1983).

The common feature of all of these mechanisms of tolerance is that the response to subsequent drug administration is changed. Depending upon the nature of the particular response, the tolerance might be evidenced by a change in the effective dose, the lethal dose, the time course of the drug effect, the range of effects, or some combination of these. Furthermore, the changes that occur within one system can even alter the future responses to drugs that are in a different pharmacological class (cf., Glowa & Barrett, 1983). We turn now to some specific examples of tolerance to demonstrate some of these reactions to repeated drug injections.

Tachyphylaxis

The term tachyphylaxis literally means rapid protection and is exemplified by the tolerance that develops to the effects of indirect acting drugs. Ephedrine, a drug which stimulates the sympathetic nervous system, is such a drug. As shown in Figure 9.3a, a standard dosage of ephedrine produces a rapid and short lived increase in blood pressure. If this same dosage is repeated at 10-minute intervals, the effect becomes smaller and smaller until, after several dosages, there is virtually no change in blood pressure. How could such a rapid tolerance develop?

The mechanism of this rapid tolerance can be inferred by the time course and by the effects of other drugs. The tolerance does not represent a permanent change, because the change in blood pressure will return to its original level if an interval of several hours is allowed between doses. This pattern of rapid tolerance that goes away quickly could be the result of fatigue of the smooth muscles that cause the vasoconstriction. However, the effects of epinephrine show that this is not the case. Repeated dosages of epinephrine continue to produce large elevations in blood pressure, and a single dosage of epinephrine given at a time when ephedrine has no effect, will produce a full scale change in blood pressure (see Figure 9.3b).

The interaction of these drugs with a third drug, reserpine, provides further information about the mechanism of tachyphylaxis. Reserpine causes the gradual depletion of norepinephrine from the sympathetic terminals. This results in a decline in blood pressure, which can be readily reversed by epinephrine. By contrast, ephedrine (even the first dosage) has no effect on blood pressure after the transmitter substance has been depleted (see Fig. 9.3c).

The conclusion is that the tachyphylaxis is the result of a rapid emptying of the transmitter substance from the synaptic vesicles (see Figure 9.3d). Ephedrine per se has no direct effect on the smooth muscle receptors that mediate the change in blood pressure. Rather, the elevated blood pressure is produced indirectly by stimulating the release of the neurotransmitter from nerve terminals. Repeated dosages of the drug in rapid succession release the transmitter faster than it can be replaced, and the effectiveness of the drug declines. These conclusions are further supported by the observations that norepinephrine administration not only produces an increase in blood pressure, but it also partially restores the effectiveness of ephedrine. The restoration occurs because the reuptake process (cf., Chapter 3) incorporates some of the norepinephrine into the vesicles where it can be released by the next dosage of ephedrine.

This form of tachyphylaxis is a special case of tolerance that does not involve any particular reaction of the systems involved. It is a simple case of the drug effect being limited by the capacity of the system to respond. The remaining types of tolerance that will be discussed involve a much more dynamic and longer lasting reaction to the effects of drugs.

Changes in Receptor Sensitivity

Tolerance can also be mediated by a change in the sensitivity of the relevant system to the drug or

transmitter. An example of this sort of tolerance can be seen in the results of an experiment performed by Brodeur and DuBois in 1964. They administered daily dosages of an acetylcholinesterase inhibitor to rats. This blockade of the inactivation of acetylcholine allows the transmitter substance to accumulate. Initially, these drug injections produced a variety of parasympathetic symptoms, including tremor and convulsions. By the end of 60 days, however, tolerance had developed and none of these effects was observed.

There are several possible ways that such tolerance could be developed. For example, the drug could lose its ability to block acetylcholinesterase. However, assays demonstrated that the degree of cholinesterase inhibition remained unchanged over the 60-day treatment period. This leaves open the possibility that the acetylcholine levels were brought under control by some other mechanism, but measures of acetylcholine showed the same high levels were produced by the drug on Day 60 as on Day 1. How could tolerance develop if the actions of the drug remained constant?

Suppose the observed tolerance occurred because the neural systems had become refractory to the high levels of acetylcholine. This notion was tested by administering carbachol, a synthetic drug that acts on receptors for acetylcholine, but is immune to the inactivating effects of acetylcholinesterase. In animals that had not received prior drug treatment, the LD-50 was 2 mg/kg. The rats that had developed tolerance to the cholinesterase inhibitor were twice as resistant to the effects of carbachol, showing an average lethal dose of 4 mg/kg. In other words, the drug continued to inhibit the action of acetylcholinesterase, the resulting increase in acetylcholine levels were maintained, but the tremors and convulsions disappeared: The drug actions remained constant while the drug effects declined.

The most likely mechanism for this form of tolerance is a change in the sensitivity of the postsynaptic membrane. This can occur through the process of neuromodulation (see figure 9.4). Synaptic activity is a dynamic process, which can be controlled by either a change in the amount of transmitter substance that is released or a change in the response to the transmitter. In the example described above, it would appear that the neural systems responded to the high acetylcholine levels by reducing the number of receptors (cf., Schwartz and Keller, 1983).

Although it is not necessary to go through the details of a specific example, it should be pointed out that the same mechanisms can result in tolerance to drugs that produce a decrease in transmitter substance. The initial effects of transmitter reduction are typically greater than the chronic effects. This type of tolerance can be attributed to an increase in the number of postsynaptic receptors. This effect has been described in earlier discussions as it applies to the phenomenon of denervation supersensitivity. The increased sensitivity that follows nerve damage can be viewed as tolerance to the physical damage.

These changes in receptor populations involve some rather major commitments of cellular metabolism. As such, they have the properties of both inertia and momentum; it takes some time (perhaps days or weeks) for the tolerance to develop and perhaps even more time for the system to return to initial levels when the drug is no longer present. These are very important considerations which will be seen in more detail in the later discussion of rebound phenomena.

Enzyme Induction

Enzymes are protein molecules that increase the speed of chemical reactions. They typically have a rather high affinity for a particular chemical structure (the substrate) and the enzyme-substrate complex proceeds through the chemical reaction faster than the substrate alone. We already have seen several examples of enzymes that are involved in neurotransmitter systems (e.g., AChE, MAO, COMT and tyrosine hydroxylase). The liver has a rather extensive library of enzymes that facilitate physiological processes (especially digestion) and help to break down toxic substances from both internal and external sources.

The chemical specificity of enzymes allow for the precise control of chemical reactions, but it also poses a problem. It would be very inefficient (not to mention impossible) for the body to produce and store all the enzymes that might be needed. It would be much simpler to have a way to limit production to those that actually are needed. This is what happens in the process known as enzyme induction (see Figure 9.5). When a new foodstuff or drug is encountered it may induce the metabolic machinery to produce an enzyme that has the specific ability to break it down into simpler components that can be used by the body (in the case of foodstuffs) or inactivated and eliminated (in the case of drugs).

The induction of enzymes involves protein synthesis, a process that may require several hours or more to take place. What this means in terms of the metabolic fate of drugs is that the drug molecules from the first injection may induce the formation of the appropriate enzyme (usually by liver cells), but undergo metabolism through the existing, sluggish pathways. Thus, the drug may stay in the system and produce its effects for a long period of time. However, once the liver cells have begun production of the enzyme, it is more readily available for encounters with the drug molecules, and the breakdown reactions for subsequent dosages will proceed more rapidly. It should be noted that this is not an all or none process, but rather one which can be regulated by the number of times the inducing substance is encountered and the amount that is presented. In any event, the induction of enzymes can result in dramatically different rates of drug metabolism that are seen as examples of tolerance.

The barbiturate drugs provide a good example of tolerance that is at least partially the result of enzyme induction. Remmer (1962) administered high anesthetic doses of pentobarbital to rats on three successive days. Rats in a control group received daily injections of saline. Then all the rats received a lower test dosage to determine if tolerance had developed. The rats that had been pre-treated with pentobarbital slept only half as long as the rats in the control group (30 min vs 67 min). This change in sleeping time was paralleled by a change in the rate of eliminating the drug from the system. The half-life of the drug (the time required to inactivate half of the injected drug) in the control group was twice as long as that of rats that had been pre-treated with pentobarbital.

It could be postulated that the relevant brain cells became less responsive to the effects of pentobarbital in the same way that the cells became less responsive to acetylcholine in the previous discussion. The evidence does not support this. The concentration of pentobarbital in the blood at the time of awakening

can be used as an index of the sensitivity of the cells to the drug. As the concentration gradually falls, it eventually reaches a level that is low enough to allow the animal to awaken. The rats that had been pre-treated were at least as sensitive to the drug as control rats, with waking levels of the drug that were even slightly lower than those of the control group.

The phenomenon of enzyme induction can produce a dramatic tolerance in terms of the effective dosage of a drug, but it does not necessarily confer the same degree of protection against lethal dosage. It fact, the LD-50 can remain virtually the same, while tolerance increases the requirements for an effective dose (the ED-50) until it may be almost identical to the lethal dose. Let us examine this curious phenomenon more carefully with a hypothetical extension of the pentobarbital tolerance shown above.

The upper panel of Figure 9.6 shows the normal course of a barbiturate drug. After injection, the drug is rather quickly absorbed into the plasma compartment. When a certain concentration is reached, sleep ensues while the drug levels continue to rise and produce a deeper level of anesthesia. Eventually, the drug will reach its peak concentration, which is determined by the amount of drug, route of administration and other factors discussed in Chapter 3. Meanwhile, the drug is being metabolized and the plasma concentration begins to decline. When it reaches a certain level, the animal awakens and the drug metabolism continues until the drug has been eliminated from the system.

After several exposures to the drug, the enzyme that degrades the drug has been induced, and the drug is removed from the system more rapidly (Figure 9.6b). This shortens the sleeping time by allowing the animal to awaken more quickly. However, the onset of sleep and the peak concentration of the drug in the plasma may show little or no change if the absorption of the drug is fast relative to the drug metabolism.

Now, suppose an attempt is made to duplicate the original drug effect (60 min of anesthesia) by increasing the drug dosage. The faster rate of drug metabolism requires a very high dosage to forestall awakening for the full hour. In this hypothetical case (see Figure 9.6c), the peak plasma levels are very near the lethal dosage.

With the margin of safety (the ratio of the LD-50 to ED-50) reduced by tolerance, it may be advisable to administer multiple doses over time (e.g., a supplemental dosage every 20 min) to attain the same duration of action (see Figure 9.6d). These effects demonstrate that tolerance can render a drug considerably more dangerous, a finding that has important implications in the clinic, the laboratory, and on the street.

Rebound Effects

The various types of tolerance are, in some sense, an extension of the concept of homeostasis. The physiology of the organism reacts to a challenge by attempting to return the system back to normal. In the case of drugs, this can have important consequences not only for the changes in the effectiveness of

the drug, but also for the rebound changes that occur when the drug is no longer present.

The rebound phenomena can be observed readily in the case of nicotine and caffeine. On the surface, it would seem that individuals who use these relatively mild CNS stimulants should be easily identifiable. They should, perhaps, have faster reflexes, be more vigilant, require less sleep, or be more aware of the environment. Or perhaps they should be more irritable, anxious, or jumpy. None of these effects, positive or negative, is observed. Virtually every attempt to extract an identifiable difference in physiology or personality between smokers, coffee drinkers, and nonusers has failed. The differences are revealed when these groups are compared without drug. The details of the effects are complicated, but nearly everyone has seen or been either a coffee drinker before the first cup in the morning or a smoker trying to quit. The major effect of these stimulant drugs is not to produce an average state of arousal that otherwise could not be attained, rather they come to prevent the rebound effects that would occur without the drug (sleepiness, lack of energy, dysphoria, etc.). The mechanisms of tolerance actively counterbalance the effects of the drug, and this balance can be unmasked by removing the drug from the system (see Figure 9.7).

The rebound effects can be considerably more serious than a little early morning grumpiness. The chronic, heavy use of CNS depressant drugs such as barbiturates or alcohol can set up dangerous counter-effects. When these effects are released by the abrupt withdrawal from the drug, hyperexcitability occurs, which in severe cases can lead to convulsions and death. With chronic, heavy use of alcohol, this rebound hyperexcitability may be seen as largely irreversible motor tremors, especially of the hands (the DT's or delirium tremens). These rebound effects are most pronounced when the drugs are withdrawn abruptly after a period of sustained high dosages, but this is not a prerequisite. So swift is the body's ability to counter these drugs that a single dosage can set up rebound effects. An overdose of alcohol or barbiturate first presents the danger of death through its depressant effects, followed by the susceptibility to seizure activity that may be equally dangerous. It is for this reason that the most superficially obvious treatment of barbiturate overdose-- the administration of stimulant drugs such as strychnine or picrotoxin-- is contraindicated.

Rebound effects are also major factors in the use of amphetamine and related drugs. The actions of amphetamine are complicated and include both direct effects on the postsynaptic receptors and the indirect release of the neurotransmitter substance from the presynaptic vesicles. The behavioral effects include increased arousal, greater physical energy, a heightened sense of well being, and even euphoria. Tolerance to these effects occur readily and probably include all of the mechanisms (transmitter depletion, receptor changes, and enzyme induction) that were discussed above. A common sequel to the stimulant properties of amphetamine is a profound depression, the depth of which is related to the amount and duration of the drug administration. In practice, it is almost impossible to avoid the rebound phenomena. In part because of the indirect actions of the drug, the effects tend to be self limiting, with the depletion of transmitter rendering the drug ineffective until a period of time has been allowed to restore the system toward its previous state.

B. BEHAVIORAL CONTRIBUTIONS

In studying drug actions and drug effects, it is sometimes easy to forget a basic fact about the physiology of the nervous system: It was not designed for the purpose of responding to drugs invented or harvested by man. The actions of drugs can magnify, interrupt, speed up and delay, but the processes are those that are inherent to normal functions and the maintenance of the brain and behavior. Accordingly, we must not limit the phenomena of tolerance and withdrawal to the realm of drug use, but must search out the relevance to normal functions. Neurotransmitters can be viewed as endogenous drugs and they surely trigger their own neuromodulatory and rebound effects. We turn now to some situations in which behavioral processes impose dramatic limits on the effects of both drugs and environmental situations.

Behavioral Tolerance

The phenomenon of tolerance can be no simpler than the actions of the drug to which tolerance is developing. One of the fundamental principles of pharmacology is that no drug has a single action (cf., side effects in Chapter 3). The extended implication of this is that no drug can induce a single type of tolerance. If a drug has a major effect and two distinct side effects, then it is very likely that tolerance can develop to each of these independently. In some cases, this can be the determining factor in the development of a drug for clinical use. For example, if tolerance develops to a troublesome side effect within a few days or weeks, then the patient may be able to benefit from the long term use of the drug. On the other hand, if tolerance develops to the main effect, but not the side effect, then the drug becomes less and less useful over time.

The development of tolerance to specific aspects of drug action may present some difficulties, but the picture becomes still more complex when behavior is considered. In the previous section, we developed the notion that behavior per se could be likened to a drug, triggering rebound effects comparable to those occurring in response to the administration of drugs. We turn now to a consideration of behavioral contributions to drug tolerance and present some of the most intriguing findings in the pharmacological literature.

The development of tolerance to the effects of a drug poses some of the same problems of interpretation that are encountered in the recovery from brain damage. In both instances, the initial effects frequently are more pronounced than the long term effects. In the case of brain damage, the problems of interpretation are particularly intractable. Does the recovery of some of the lost function reflect the "take-over" by a related area of the brain? Is it due to some neuromodulatory effect such as denervation supersensitivity? Or, is it the result of learning to accomplish the same behavioral goal in a different fashion? There is evidence to support each of these possibilities, but the conclusions remain tentative because of the permanence of brain damage.

As researchers began to look more and more carefully at both tolerance and recovery, some confusing observations began to appear. In some cases, clear recovery of function following brain damage could be observed on one task but not another. Likewise, drug tolerance could sometimes be observed in one measure but not another. There was something missing in the interpretation of these effects. Fortunately,

most drug effects are considerably less permanent than brain damage (although some of the tolerance and rebound effects may be very long lasting) and can be administered repeatedly. This opens the door for experimental approaches that can better answer some of the questions posed above.

Pre-Post Design

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One of these approaches, known as the pre-post design, can be used to demonstrate the phenomenon known as behavioral tolerance. A series of experiments by Carlton and Wolgin (1971) exemplify this approach. The rats in these experiments received a restricted diet of food pellets and were given a daily period of access to a drinking tube that contained sweetened condensed milk. After several days, the amount of milk that was consumed during this period stabilized and served as a baseline for the drug and drug tolerance effects. If amphetamine was injected a few minutes before the daily test session, the milk consumption was greatly reduced. However, if rats received amphetamine injections before each daily session, the rats drank a little more milk each day until, by the end of the two-week experiment, the rats that received amphetamine were drinking as much milk as the control rats that received saline injections. Thus, tolerance had developed (see Figure 9.8).

The most obvious explanation of the increase in milk consumption is that one of the pharmacological tolerance mechanisms described above had taken place to reduce the effectiveness of the drug. Another possibility, however, is that the drug actions remained essentially the same, but that the animals made a behavioral compensation that allowed them to drink the milk despite the drug effects. The pre-post design allowed a test of these alternatives by comparing the milk consumption of the following treatment groups:

Group CON: Saline injections before each session

Group PRE: Amphetamine injections before each session

Group POST: Amphetamine injections *after* each session

The critical treatment group is the one that received the amphetamine injections after each session. Obviously, the drug cannot be influencing the milk consumption before it is given. (It could influence the consumption during the next session, 23 hr later, through residual effects of the drug or through conditioned aversion effects, but these possibilities were controlled for in the complete design of the study.) Even though the measure of milk consumption was taken deliberately in the "wrong" place, one would still expect that pharmacological tolerance would be developing to the amphetamine. Enzyme induction could occur, the number of receptors could be changed, the amount of neurotransmitters could be changed, or some combination of these could occur. But the measure of milk consumption would be blind to these effects because it was taken long after the drug was given (23 hr).

The critical test occurred after these mechanisms of tolerance were given an opportunity to develop. The rats that had been in Group POST now were given a test dosage of amphetamine BEFORE the milk consumption. If tolerance to the amphetamine had been developing, as it had in the rats in Group PRE, then the milk consumption should have remained at the baseline level (see Figure 9.8). Instead, the milk intake was substantially reduced! How could tolerance to amphetamine develop for one group of rats but not the other? The answer (although it does not specify a mechanism) is behavioral tolerance: the rats in Group PRE became tolerant to the effects of amphetamine on milk consumption. Although pharmacological tolerance may have developed over the treatment period, this was not sufficient to block its effects on milk consumption. The necessary component was behavioral experience while the drug was in effect. The rats, in some sense, had learned to consume milk despite the effects of amphetamine.

A comparable experiment has been done by Campbell and Seiden (1973) using performance of a drl task to assess the effects of amphetamine. The performance of this task, which requires low rates of responding, is severely impaired by the effects of amphetamine. However, tolerance develops with repeated injections, and the behavior returns to the normal baseline that was obtained without drug. Again, the pre-post test design showed that this return of normal behavior could not be attributed to pharmacological tolerance. Rats that had received repeated injections of amphetamine, but without the opportunity to perform the drl task while under the influence of the drug, still showed serious impairment when the drug was given before the drl test session.

The results of these experiments suggest some clinical considerations that probably have not received the attention they deserve. The amphetamines and related compounds are widely used by dieters in both prescription and over the counter formulations. The long term effectiveness of this therapy is marginal at best. It seems likely that humans, as well as rats, develop behavioral tolerance and learn to consume the good things in life (including sweetened condensed milk) despite the effects of the drug.

One possible explanation of behavioral tolerance is that it somehow blocks out the ability to perceive the effects of the drug. This is probably not the case. Bueno and Carlini (1972) showed that the ability of rats to climb a rope was impaired by THC (the active component of marijuana). After tolerance developed, the rats were able to climb the rope as well as control animals, but were nonetheless capable of discriminating (in a different task) the presence or absence of THC.

Environment and ritual

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One of the most dramatic demonstrations of the power of behavioral tolerance has been demonstrated by Siegel and coworkers (1982). The repeated administration of opiate drugs produces a remarkable degree of tolerance. In order to maintain the same level of analgesia over a period of days, the drug must be administered in ever increasing dosages and can reach levels that may be several times higher than the

LD-50 established for naive animals. These investigators administered a schedule of increasing dosages of heroin working the rats up to a dose that they could not have initially tolerated. Half of the rats had received this series of injections in the colony room. The other half of the rats were removed from the colony to a test room that differed both visually and by the presence of a 60 dB white noise, where they received their injection of heroin. As expected, all of the rats withstood the increasing dosages of heroin.

After completing this series of increasing dosages, the rats were given a single test dosage of 15 mg/kg of heroin. This is a very large dosage of the drug, being close to the LD-100 (96% mortality) for rats that have had no experience with the drug. Rats that had received the series of heroin injections showed a substantial increase in the ability to withstand the drug, with only a 32% mortality rate. However, a large portion of this protective effect was attributable to behavioral rather than pharmacological tolerance. If the rats received the same injection, but simply in a different room (colony rats in noise room; noise room rats in colony), they were twice as likely to die (64%). The association of a particular environment with the administration of a drug adds to the ability to compensate for the effects of the drug. In this case, the learned aspects of the tolerance can literally mean the difference between life and death.

Siegel proposes that many of the deaths that occur through drug overdose have a behavioral component. Addicts frequently develop ritualistic behavior associated with the administration of a drug (same place, same people, etc.) When this ritual is changed, for example, by purchasing the drugs on the streets of another city, the likelihood of death through overdose is increased. The common explanation that the drug obtained was more potent than that usually used may be true in many cases, but the behavioral component may be a major factor as well.

How is it possible for an animal to behaviorally reduce a drug effect? Some of Siegel's earlier work provides a possible answer to this question (Siegel, 1975). The work centered on the possibility of the Pavlovian conditioning of drug effects. Suppose, for example that the injection procedure (the room, the handling, the insertion of the needle) is always conducted in the same manner. This set of stimuli could serve as a conditioned stimulus (CS) to predict the physiological changes (UR) that would follow as a result of the drug injection (the unconditioned stimulus, or US). What would happen after a number of such pairings if saline were substituted for the drug? The CS (injection procedure) would be the same as always, but would a conditioned response (the physiological change) be observed?

The drug under investigation was insulin, which lowers the blood sugar levels. If insulin injections are given in the same manner, is it possible to get a conditioned change in blood sugar levels that parallels the conditioned salivation that occurs when a bell has signaled the presentation of food powder? The answer is yes, but the direction of the effect is opposite that which one might first expect. Instead of getting a conditioned lowering of blood sugar, Siegel observed a conditioned increase in blood sugar. This makes perfect sense if the conditioned response is viewed as an attempt to compensate for a predicted change in the environment. Normally, the amount of insulin produced by the animal is controlled within rather narrow limits to regulate the level of glucose utilization by the cells, prepare for digestive loads, etc. The injection of an outside source of insulin disturbs this balance, and the animal must reduce its own production of insulin in an attempt to counteract this effect. According to Siegel's

results, this compensatory response can be learned, and a sham injection procedure causes a reduction in insulin and a corresponding increase in blood sugar. Of course, little or none of this is cognitive learning (try to imagine how you would voluntarily reduce your own insulin levels), but the mere fact of association is sufficient to trigger these processes according to the laws of Pavlovian conditioning.

Once again, the importance of these phenomena in the clinic should not be overlooked. When drugs that cause pronounced physiological effects are given over long periods of time, there is a very real possibility that Pavlovian learning processes may take place to counteract the effects of the drug.

Opponent Process Theory

Solomon and Corbit's theory of opponent processes is modeled after well established events that occur in the sensory systems. The most familiar of these are the negative after images that occur in the visual system. If an individual stares steadily at a relatively bright object, say a television screen in a dimly lighted room, the absence of that stimulus produces a curious illusion. When the vision is shifted to a neutral part of the room, a ghostlike image of the screen is projected onto the surface and this image is dark rather than light. Hence, the term negative after image. The negative after image is also familiar in the case of indoor photography. The bright flash of light is followed by after images (usually negative, but sometimes alternating positive and negative) of small dots that are projected onto the "real" visual world. These after images even extend into the realm of color vision, with the after images being of the complementary color (red objects produce a green after image, blue objects produce yellow, and vice versa). Comparable illusions can appear with the motor system, as evidenced by the "light-footed" feeling that occurs when a pair of heavy boots or roller skates is removed. But does it make sense to apply these principles to something as complicated as emotions? Probably yes.

There are three major components to the opponent process theory:

- Affective Contrast
- Affective Habituation
- Affective Withdrawal

Affective contrast is the most fundamental of these, and closely parallels the response of the visual system to light. The presentation of a bright light produces a peak response followed by rapid adaptation to a stable level (the A-response in Figure 9.9). When the light is turned off, a negative after image occurs and gradually dissipates with time. The magnitude of these effects is related to the intensity of the stimulus. Several observations can be cited to relate this to emotions. An infant may be lying quietly in its crib, exhibiting no particular emotion. If a nipple containing a sugar solution is offered, a positive response is obtained (the A-response). Withdrawal of the nipple results in vigorous crying (the B-

response), an effect which would not have been observed if the positive stimulus had not been presented. Comparable effects can be observed in the case of initially negative stimuli. Electric shock administered to dogs can produce an increase in heart rate. When the shock is terminated, there is a dramatic decline in heart rate and the dogs may show behavioral excitement. This is very likely the laboratory equivalent of the frenzied play activity that sometimes follows the administration of a bath to a dog (or a child, for that matter!). A more familiar example to students may be the excited chatter that frequently fills the hallways after a major examination.

The story gets more complicated with affective habituation. If a bright light is presented for a long period of time, habituation occurs and the perceived brightness is greatly diminished (the A'-response in Figure 9.9). But when the light is terminated, the negative after image is both stronger and more enduring than it was following a brief, initial exposure (the B'-response). In the laboratory, this can be observed with repeated presentation of shock to dogs. After a time, the shock no longer produces a change in the heart rate, but the "after-image" (the decrease in heart rate) becomes very pronounced. Again, the same pattern emerges in the case of human emotions: The heart throbbing, adrenergic effects of a new amour might well become a health hazard if they continued; but in the words of the songwriter, "...after 16 years of marriage, the fires don't burn so hot!" (Harry Chapin). Returning to the theory, the A'-response takes over, but the stage is set for a tremendous B'-response if the stimulus should be terminated, e.g, the grief response that follows the loss of a loved one.

The third aspect of the theory, affective withdrawal, is really just a sharpening of the concepts described by the first two. We will describe two of the numerous examples put forth by the theorists. One of these involves the sport (?) of skydiving. For the naive jumper, the period before the jump is filled with anxiety. This anxiety is galvanized into terror with the actual jump, and relief follows a safe landing. Should the individual continue this pastime, the emotions that color the experience undergo the pattern of affective habituation and contrast described above. Anxiety is replaced by eagerness, the terror is downgraded to a thrill, and relief is transformed into intense exhilaration--the raison d'etre for what would otherwise be a silly thing to do. A similar pattern can be applied to the abuse of a drug, for example, heroin. The initial presentation is preceded by a state of rest, the drug's actions produce a "rush", and the aftereffect is one of craving. With veteran users, there is a shift in the emotions, and the drug's actions produce a state of contentment (rather than a rush). This contentment (the A'-response) is followed by abstinence agony (the B'-response), which turns into an intense craving for the drug, and the drug now has only the capacity to relieve the craving rather than reproducing the initial rush-- and the circle continues (see Figure 9.10).

The opponent process model is also relevant to many of the paradoxical effects that accompany goal attainment. Reinforcement in an operant schedule does not necessarily spur the pigeon into immediate further action, but rather may be followed by a post-reinforcement pause. The attainment of a long-sought goal such as a college degree is frequently followed by a bout of depression, and the postpartum blues are almost unavoidable. Solomon and Corbit emphasize the view that all of these effects are noncognitive in nature. That is, they are not the result of a logical, cognitive analysis of the present environment, but rather are the result of a previous environment that no longer applies.

These changes may well be noncognitive, but they cannot-- if we continue our attempts to view the brain and behavior in a lawful relationship-- be nonphysical. Powerful stimuli produce powerful changes in the neurotransmitter systems, and these in turn trigger the processes of neuromodulation, changes in receptor sensitivity, and even transmitter depletion. These reactions, like tolerance to a drug, alter the responses to standard stimuli and set the stage for withdrawal reactions.

Although the opponent process theory has not gained universal acceptance, we shall risk pushing it one step further in terms of the noncognitive aspects of emotions. There will not be many students of this book who will recall the Mary Tyler Moore show, but one of the episodes provided a poignant example of opponent processes in action. A dear friend of Mary's, Chuckles the Clown, died. Of course, she was stricken with grief, and she decried all references to the lighter side of his life and career. At the funeral, however, she was overcome by an uncontrollable urge to laugh; not hysterical, unfeeling laughter, but true, euphoric, high spirited laughter. Why? The grief reaction is understandable in the framework presented above. However, the grief itself is a powerful stimulus that can set up its own opponent processes, and as grief subsides, periods of unexplainable high spirits may penetrate the prevailing negative mood (bringing with it a certain burden of guilt).

The point of all this is that the brain is a dynamic system that can respond quickly in terms of neuronal action potentials, but more slowly in terms of the chemical adjustment of the overall tonus of a transmitter system. These changes occur in direct response to the changes in the environment, but the properties of inertia and momentum do not always allow the changes to reflect, in a veridical manner, what is happening at a particular moment. An appreciation of these facts can make the emotional responses to a loss (or for that matter, a gain) a lot more understandable. Clinicians now expect a recurring cycle of mood changes following a loss such as a serious knee injury in an athlete. The first phase is one of denial that the injury is serious or that the loss will have a major impact on the individual's loss. This is followed by anger. The anger is followed by depression. The depression, in turn, may be followed by denial that may even take on a flavor of a high spirited, can-do attitude about coping with the injury. Most of these changes can be characterized as noncognitive in that they bear little relationship to the current changes in the outside environment. They are, almost literally, drug effects.

C. FOUNDATIONS OF ABUSE

Terminology

The terms drug addiction and drug abuse once seemed like eminently reasonable descriptive terms. The use of certain drugs produced a physical dependence, creating a situation in which the body required the presence of the drug to maintain normal physiological functions. This physical dependence on the drug was the basis for the individual's profound need for the drug, the addiction. These definitions worked fairly well for certain classes of drugs and drug users, but there was a growing list of instances in which the definitions seemed inappropriate. Tobacco use, for example, certainly involves craving, but the

degree of actual dependence (i.e., physiological need) is much less dramatic than in the case of morphine or barbiturates. There is virtually no danger of death or severe symptoms of withdrawal even with complete abstinence. A distinction has sometimes been made between a drug habit and a drug addiction to reflect, in a rather rough manner, the differing physiological bases that control the use of the drug. These distinctions blur, however, with differing patterns of use, and the three-pack-a-day smoker may well have a greater physiological need than the individual who manages to limit the use of morphine. The distinction is equally blurry when one tries to draw the lines between moderate drinking, heavy drinking, and alcohol addiction.

As it became apparent that the physiological measures of dependence or the amount of drug used could not clearly define addiction, new terminology began to arise. The term addiction began to give way to the term drug abuse, which suggests a greater behavioral contribution. If an individual's use of a drug is extensive enough to interfere with work, family, or lifestyle, then the drug is being abused. There are still fuzzy edges in this definition, but the term is somewhat more realistic than the term addiction, because it reflects the pattern of use as well as the amount of drug used.

There also can be some argument concerning the term drug. Almost everyone will agree that morphine is a drug, but some will balk at considering coffee as a drug, and consensus becomes even more difficult in the case of chocolate bars, nutmeg or peanut butter. This dilemma was met with yet another evolution of the terminology, and researchers now speak of substance abuse. This too shall pass: There is a growing recognition (especially with the burgeoning business of state lotteries) that behavior itself can be the object of abuse. There is a commonality among the heroin junkies, smokers, coffee drinkers, beer drinkers, gamblers, overeaters, workaholics, and maybe even runners. They are neither inherently evil nor necessarily burdens on society, but they are all caught, to some degree, in a behavioral and pharmacological trap. We turn now to an examination of this trap.

Self Administration

Although physiological dependence may not be essential for addiction or abuse (cf., Bozarth & Wise, 1984), it certainly can be an important contributor. This is most easily seen in laboratory models of addiction in which animals are given the opportunity to self administer drugs. In some cases, the animals may simply be given access to a solution that contains the drug and allowed to freely ingest the substance. More commonly, the drug is used as a reinforcer in an operant conditioning situation as shown in Figure 9.11. A catheter may be permanently implanted into a blood vessel (e.g., the jugular vein or carotid artery), with provision made to connect the catheter to an outside source via a small tube. When the animal has fulfilled the requirements of the schedule of reinforcement, a small amount of drug is injected as a reinforcer.

In general, there is a fairly close correspondence between the list of drugs that are abused by humans and the list of drugs that animals will self administer in the laboratory. Among these are the opiates, the barbiturates, amphetamines, and some hallucinogens. The drugs that can be used as reinforcers appear to have three characteristics in common:

- They act on the CNS.
- The CNS effects occur rapidly.
- After continued use, withdrawal results in rebound effects.

Reinforcement restructured

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The behavior of a rat in a self administration experiment shows many parallels to drug use in humans. In the case of morphine, for example, the initial rate of pressing the lever to obtain the drug may be very low. Gradually, over a period of days and weeks, tolerance to the morphine begins to develop (this can be demonstrated by independent testing of pain thresholds) and the lever pressing shows correspondingly greater rates in order to inject the greater amount of drug that is required to produce the "desired" effects. If the rat is given a dosage of morphine via a standard injection procedure, the amount of lever pressing is greatly decreased for the duration of the drug effect. If the rat is removed from the apparatus and withdrawn from the morphine for a period of time, physical withdrawal symptoms will be seen, and if the rat is returned to the apparatus, very high rates of lever pressing may be observed as the animal restores the morphine levels.

The administration of morphine under laboratory settings not only parallels some of the features of human drug use, but also parallels some of the aspects of conventional drives and reinforcers. As in the case of food and water, the drug can serve as a reinforcer for operant behavior. If the reinforcer is given outside of the operant setting, there will be a corresponding decrease in lever pressing, while withdrawal from the reinforcer will result in higher rates of responding when the subject is returned to the operant chamber. But there is an important difference. The drug not only acts as a reinforcer, but sets the stage for the development of the motivation to obtain the drug. Presumably, the rat has not had a lifelong yearning to obtain morphine, nor can we attribute the initial lever pressing to peer pressure or the ills of society. The first dosage of morphine appears to have some immediate reinforcing value, but more importantly, it initiates a chain of physiological events that now result in a deprivation state that was not there before: The absence of morphine is aversive. Eventually, the positive rewarding effects of morphine may pale in comparison to the aversive effects of not having the drug, and the resulting behavior may be more akin to avoidance behavior than responding for reward.

Not all drugs that have abuse potential show such close parallels between human usage and laboratory models. Researchers have found that it is almost embarrassingly difficult to get laboratory animals to consume alcohol. The taste is sufficiently aversive to the naive palate to prevent consumption in amounts that lead to tolerance, rebound effects, etc. It is usually necessary to coerce the animals to consume the alcohol by making it a part of their required food or water supply. However, once the

alcohol consumption has been established, the animals will readily and voluntarily maintain the "habit". But why should it be so difficult to establish alcohol abuse in the rat while it is so difficult to prevent it in man? There is no simple answer to this question, but a more careful analysis of the drug administration procedures may provide some important clues.

Environmental bridges

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Goldberg and associates (1981) performed an experiment in which monkeys were given the opportunity to press a lever to obtain a small intravenous injection of nicotine. Although the monkeys pressed the lever enough to receive a few injections (thereby having the opportunity to experience the drug effects), the rate of pressing did not increase, but rather remained at the low level that was shown by a control group that received saline injections. Again, the failure to demonstrate self administration was curious in view of the ability of nicotine to reinforce behavior in humans. These investigators made a clever extension of their results in a second experiment: Whenever the rats earned a reinforcement, it resulted in both the drug injection and the change of a green light into amber as the subjects entered a 3-min period of darkness during which time the drug effect developed. This additional stimulus had no effect on animals that were receiving saline injections, but greatly enhanced the self administration of nicotine.

Why should the addition of an external stimulus aid the establishment of a nicotine habit? And even if it works, does it not belittle the results somewhat to have to resort to this sort of a crutch to demonstrate the drug administration? The answer to both questions may be found in a series of experiments performed by Snowden (1969). There was some controversy about whether the regulation of the amount of food eaten is controlled by the acts of chewing, tasting and swallowing, or by monitoring the caloric feedback from the food in the stomach. One way of testing these alternatives was to place the rat in a situation in which all nutrients were obtained by pressing a lever to inject liquid diet directly into the stomach. This procedure is directly comparable to that used for the self administration of drugs, and most experiments demonstrate that the rats are remarkably accurate in controlling the overall calories that are ingested in this manner. But Snowden showed that the results were not as clear-cut as they seemed. The liquid diet is prone to spoilage in these long term experiments, but the problem can easily be avoided by keeping the reservoir in an ice bath. This prevents the spoilage, but when the rat earns a reinforcement, it receives not only a small amount of diet in the stomach, but also experiences a cool tactile sensation as the liquid passes through the tube under the skin of the head and neck en route to the stomach. When Snowden warmed the liquid to body temperature before it reached the skin, the ability of the liquid diet injections to serve as a reward was greatly diminished. Why should this happen?

In both cases, the reinforcing value of a substance was enhanced by the addition of some external stimulus. The most likely explanation of these results is that the external stimulus helps to bridge the gap in time between the physical delivery of the reinforcer and the actual physiological change that results. In the real world and most laboratory situations the presence of these external mediators are the rule rather than the exception. The sight, smell, taste, and texture of food are all powerful reinforcers that

signal the ultimate physiological reward, caloric energy. In terms of the immediate ability to control behavior, these harbingers of physiological change are more important than the real change. When the situation is so tightly controlled that only the physiological change can be experienced, the reinforcing value is greatly diminished. The situation becomes, in a sense, a Pavlovian delayed conditioning procedure which is successful only after many trials, if at all.

The picture that emerges is that environmental cues and behavior are an inextricable part of drug effects and of drug abuse. These behaviors become an important part of the overall pattern of abuse, even when the drug action is so fast that an external stimulus is not essential to bridge the gap. Consider, for example, the administration of nicotine by cigarette smoking. How does a drug that requires an environmental bridge in the laboratory gain such control over so many people in the natural environment? One reason is that the route of administration is ideal in terms of the speed of the effect. The inhalation of nicotine in tobacco smoke produces very rapid effects, reaching the brain within 8 seconds (Jaffe, 1980). This is even faster than an intravenous injection into the arm, and is fast enough that each puff of the cigarette can produce a discrete, detectable drug effect! This rapid delivery of distinct reinforcements serves not only to maintain the behavior, but also provides an excellent environment for the development of secondary reinforcers of associated behaviors such as manipulation of the cigarettes, oral contact, the smell of the smoke, and specific times and places (e.g., after meals, while driving, while reading the paper, etc.)

Environmental and behavioral cues are not only important contributors to the rewarding effects of drugs, but also to the motivational states that direct the organism toward specific drug effects. Certainly, a major aspect of these motivational states can be attributed directly to the physiological actions of the drug. The effects of enzyme induction, neuromodulation and rebound phenomena all contribute to an internal environment that can be "corrected" by an additional dosage of the drug. But certain aspects of these physiological changes can be influenced by learning, as we have already seen in the cases of insulin or morphine injections. Stressful environments may be especially potent in this regard because of previous situations in which engaging in the rewarded behavior (e.g., smoking a cigarette) has led to a rapid, rewarding effect. The rewarding effects may be even more pronounced with a drug such as alcohol, which has some inherent properties of anxiety reduction.

It is even possible to go a step further in the analysis of environmental cues and show that these are important not only in helping to mediate the motivational state and the rewarding effects, but also in contributing to the behavioral outcome of the drug use. A particularly intriguing example of this has been shown in a clever experimental design that was developed by John Carpenter (cf., Marlatt & Rohsenow, 1981). This design unveiled the phenomenon that has come to be known as the Think-Drink effect. The critical feature of the design was the development of a cocktail that tasted the same with or without alcohol. The recipe was four parts tonic water, one part vodka, and one part lime juice. The nonalcoholic version of this was simply five parts tonic water and one part lime juice. Preliminary tests showed that the identification of these two recipes was at chance levels, the protestations of the seasoned drinkers' palates notwithstanding. The design of the experiment, shown in Figure 9.12, was a 2 X 2 design in which the subject either received alcohol or not and were told that they were receiving alcohol

or not. Thus, some of the subjects expected the effects of alcohol when it was not present, while other were not expecting the effects of alcohol when it was present. The behavioral measures (including social aggressiveness, talkativeness, motor coordination, and others) showed that the behavior was more closely related to what the participants thought they were drinking than to what they actually were drinking! Obviously, alcohol is a real drug, and with large dosages there is no way to think one's way to normalcy. However, the results of these experiments suggest that much of the stereotyped behavior associated with alcohol use may occur before the physiological effects are present or at doses which would not be sufficient to produce the behavior directly, and there is also evidence for behavioral tolerance when specific behaviors are practiced under the influence of the drug (e.g., Wenger et al, 1981).

The environmental factors become especially important when a distinction is made between use and abuse of drugs. Alcoholism is certainly one of the most costly of society's ills. The obvious solutions of voluntary abstinence or legal prohibition seem not to work. Accordingly, many researchers have turned their attention to the causes of alcoholism. One of the most interesting set of findings is that there are some subcultures that use a fairly large amount of alcohol, but have very low incidences of abuse (e.g., Aronow, 1980). Several features of alcohol use seem to be common among these groups. Children are exposed to alcohol and use alcohol at an early age, usually in the form of wine or beer as part of the meal. The parents do not become inebriated and there are strong sanctions against those who do. Inebriation is never viewed as something humorous or daring. The use of alcohol in moderation is simply taken for granted, with neither positive nor negative attributes attached. A glass of wine can be accepted or refused with the same impunity as one accepts or refuses a slice of bread. This contrasts sharply with the more traditional Middle America pattern that prohibits the use of alcohol in the young, while viewing inebriation as a source of humor ("Did you hear the one about the drunk who...") and the ability to drink as a sign of adulthood, authority and power. As children approach adulthood (or as they want to approach adulthood), they surreptitiously obtain and consume alcohol, usually in excess and almost always under conditions of stress--the perfect conditions for establishing the use of the drug for the purposes of aggrandizement and stress reduction.

Breaking the Cycle

One of the greatest ironies of humanity is that almost everyone assumes free will and control over behavior while, at the same time, ruing the fact that they cannot stop smoking, overeating, drinking coffee, gambling, drinking alcohol, taking tranquilizers, or biting fingernails. Breaking these so-called habits is one of the most difficult areas of behavior. There are those who claim it is simply a matter of will power and that they could stop at any time they really wanted to. Indeed, some do, but the rate of recidivism is high. One of the main reasons for the high rate of returning to the habit is that it has been linked to stressful situations. Abstinence is itself a stressful event, and only serves to increase the likelihood of the behavior, especially during the early stages. Schachter has claimed (on the basis of informal surveys; 1982) that the statistics are unnecessarily pessimistic because they are based upon individuals who seek professional help. His observations suggest that there are many individuals who lose weight or give up smoking without professional help and with considerably lower chances for

returning to the original patterns of behavior. Whether or not these observations will hold up under more rigorous scrutiny, it is clear that there are many cases in which the behavior is especially intractable. There is no clear formulation that can guarantee success in the attempt to break drug abuse patterns, but several suggestions can be made, based upon the way in which the abuse pattern has been established and maintained.

1. Change the US effects of the drug

If drug use is viewed as a straightforward example of conditioning, then the rewarding drug effects can be considered as the unconditioned stimulus or US. One of the more obvious ways to interfere with this chain of events is to change the effects of the drug. Perhaps the best known example of this is the drug known as Antabuse, which interferes with the metabolism of alcohol. The ingestion of alcohol causes severe gastrointestinal illness when this drug is present, and it is necessary to refrain from taking Antabuse for about three days before alcohol can be consumed without experiencing these ill effects. This drug has been used with some success in clinical settings, but one of the obvious drawbacks is that the individual must take the Antabuse on a regular basis.

Another example of interference with the US effect is the substitution of methadone for heroine abuse. The methadone is not without its own potential for abuse, but the cravings for the drug and the withdrawal effects appear to be somewhat less severe and (perhaps most importantly) it is usually prescribed under careful conditions in known quantities and purity.

A third example is somewhat akin to fighting fire with fire. One of the ways in which smokers have been aided in breaking the cycle of smoking cigarettes is to produce the drug effects via a different route. Chewing gum that contains nicotine can produce the drug effects without engaging in the sequence of behaviors that has been established by smoking. Others may turn to what is by most standards (baseball players excepted) the even less socially accepted habit of taking snuff or chewing tobacco (Will restaurants adopt spitting and non-spitting sections?) Social customs aside, these are valid methods of interrupting the cycle, because it provides for the first time, a separation between the behavioral patterns and the drug effect. If it is properly guided (and there is always the danger of substituting one habit for another, or even adding one habit to the other), the individual can eliminate many of the behavior patterns without suffering the physical symptoms that might accompany abstinence.

2. Change the reward structure

To some extent, this category overlaps with the previous one, but there are ways in which the reward structure can be changed to aid in reducing some of the behavioral components of the pattern. One way which has been moderately successful (although care must be taken to avoid nicotine poisoning) is forced smoking. The individual is forced to rapidly smoke one cigarette after another, rather than leisurely puffing away in the normal manner. This has two consequences: It usually causes some degree of discomfort due to the rapid effects of the high dosage (thereby associating aversive consequences

with the behavior of smoking), and it again allows a way in which the drug effects can be obtained under unusual circumstances.

This general type of technique has also been used in the case of food abuse (overeating) by attempting to limit eating strictly to mealtimes under rigid conditions.

3. Change the environmental cues

One of the hallmarks of substance abuse (it is unfortunate that the phrase abusive behavior has the wrong connotation) is that it involves a high degree of ritualization-- the cigarette after breakfast, the drink or two after work, the pretzels while watching TV. An important part of any program to eliminate habitual behaviors is to change these environmental cues whenever possible. This may involve a new schedule, such as skipping breakfast or eating breakfast at a later hour, avoiding certain locations, moving the TV to a different room, changing a work schedule, etc. Usually, this is not easy. There are too many restrictions in most lifestyles to allow very major changes. One of the major advantages of a formal clinical setting is also one of the major disadvantages: On the one hand, the new, controlled environment is a tremendous aid in helping to interrupt the patterns of behavior that have maintained the pattern of abuse. On the other hand, once the behavior has been changed and the patient leaves, it is very likely that the return to the previous environment will re-trigger all sorts of cues that have supported the habit in the past. Clinical psychology (and medical practice, for that matter) would be much simpler if the patients did not have to return to the causes of their disorders when they left the couch.

4. Avoid using the drug

This is an obvious truism, but it is mentioned here because of some recent controversy concerning alcohol consumption. Several different support groups, most notably Alcoholics Anonymous, have long advocated complete abstinence once the drinking behavior had been disrupted. Their view is that there is never a cure, and that any drinking will reestablish all of the behavioral patterns of abuse. It has been suggested that this requirement may be a bit too Spartan, and that controlled drinking might be allowable (cf., Sobell & Sobell, 1978). This seems not to be the case: In a follow-up study of 20 alcoholics who participated in the controlled drinking experiment (Pendery et al, 1982), the following dismal results were found: 1 was successful, 8 continued to have drinking problems, 6 returned to abstinence voluntarily, 4 died, and 1 was missing.

The presence of the drug in the body not only serves to reactivate some of the metabolic systems that were changed through previous exposure, but also recreates internal conditions that have been strongly associated with the relevant behavior patterns that supported the pattern of abuse. Apparently, truisms prevail.

D. SUMMARY

Principles

1. The effect of a drug can be decreased or increased by changing the access of the drug molecules to the receptors, or by setting up a physiological opposition to the drug.

2. The mechanisms of tolerance (or sensitization) can change nearly any feature of the drug's actions.

3. Indirect acting drugs may lose their effectiveness rapidly through depletion of the transmitter stores.

4. As neuromodulatory processes take place, the changes in receptor number or sensitivity is reflected by a gradual change in response to the drug.

5. The presence of a drug may induce the formation of enzymes that will inactivate the drug more quickly when it is administered in the future.

6. If a drug that has been present for some time is abruptly withdrawn from the system, it unmasks compensatory reactions and opposite, rebound effects may be observed.

7. The opponent process theory applies many features of tolerance to emotional responses and to some of the phenomena of addictive behaviors.

8. In some cases, the development of tolerance requires that specific behaviors occur while the drug is in effect, a phenomenon known as behavioral tolerance.

9. The pre-post design has been used to separate the effects of pharmacological tolerance from behavioral tolerance.

10. Some aspects of behavioral tolerance may be the result of the Pavlovian conditioning of compensatory responses.

11. Drug addiction, drug abuse, and substance abuse are all terms that apply to behavior that is maintained by acquired motives.

12. Self administration procedures are used as animal models of drug abuse in humans.

13. Environmental stimuli associated with drug use may serve as important bridges for the development and maintenance of habitual drug use.

14. The effectiveness of a drug may be significantly changed by the user's expectations, as in the think-drink effect.

15. The development of substance abuse may interact with normally occurring states, especially those

involving stress.

16. The drug abuse cycle may be interrupted at several points that are specified by the laws of learning.

Terms

Acetylcholinesterase

Acquired motivation

Affective habituation

Affective contrast

Affective withdrawal

Barbiturates

Behavioral tolerance

Carbachol

Compensatory response

Delirium tremens

Denervation supersensitivity

Drug effect

Drug action

Enzyme induction

Ephedrine

Half-life

Indirect action

LD-50

Negative after image

Neuromodulation

Opponent process

Pavlovian conditioning

Pharmacological tolerance

Physical dependence

Pre-post design

Rebound effects

Ritualistic behaviors

Secondary reinforcer

Self administration

Sensitization

Substance abuse

Tachyphylaxis

Think-drink effect

Tolerance

Withdrawal effects

Ablation experiment

-- an attempt to determine the behavioral changes that follow brain damage

---

Acetaldehyde

-- a toxic metabolite of ethyl alcohol

Acetaldehyde dehydrogenase

-- an enzyme that rapidly converts acetaldehyde into harmless acetic acid

---

Acetylcholine

-- a neurotransmitter of the autonomic, somatic, and central nervous systems

---

Acetylcholinesterase

-- an enzyme that rapidly inactivates acetylcholine that has been released at the synapse

---

Acetylcholinesterase inhibitor

-- a drug that blocks acetylcholinesterase, thereby increasing levels of acetylcholine in the synapse

---

Acquired motivation

-- in this context

ACTH

-- a pituitary hormone (adrenocorticotropic hormone) that stimulates the release of hormones from the adrenal cortex during stress

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Action potential

-- the electrical activity that carries information down the neuron

---

Active transport

-- a metabolic process that can transfer relatively large molecules across a cell membrane

---

Acupuncture

-- a procedure to produce pain reduction by the mechanical stimulation of nerves

---

Adenyl cyclase

-- a compound that serves as a second messenger to initiate neuromodulatory changes

---

Affective contrast

-- an opponent emotion produced by the removal of a relatively novel emotion-inducing stimulus

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Affective habituation

-- a reduced emotional response to a familiar emotion-inducing stimulus

---

Affective withdrawal

-- a strong opponent emotion produced by the removal of a familiar emotion-inducing stimulus

---

Agonist

-- a drug that mimics the effect of a neurotransmitter

Alcohol

-- a central nervous system depressant that is produced by fermentation

---

Allergy

-- an abnormally strong response of the immune system to a harmless foreign substance

---

Alpha methyl tyrosine

-- an inhibitor of the enzyme tyrosine hydroxylase

Alpha receptor

-- a specific receptor type for norepinephrine and related compounds

---

Alpha wave

-- a regular EEG pattern that accompanies quiet resting in the absence of visual stimulation

---

Alzheimer's disease

-- a degenerative disorder of brain acetylcholine systems that can accompany senescence

---

Amphetamine

-- a central nervous system stimulant that acts on neurons that release dopamine or norepinephrine

---

Amphetamine psychosis

-- the symptoms of psychotic behavior that can accompany an overdose of amphetamine

---

Analgesic

-- a drug that reduces pain

Anaphylactic shock

-- a severe allergic response that can result in respiratory collapse and death

---

Anesthetic

-- a drug that causes the loss of sensation

Anion

-- a negatively charged ion (e.g., Cl^-)

Antagonist

-- a drug that blocks the action of a neurotransmitter

Anterior cortex

-- a portion of the cerebral cortex that is a target area for the fibers of the MFB reward system

---

Antibodies

-- chemically specific molecules that are produced by B cells during the humoral immune response

---

Anticholinergics

-- drugs that specifically interfere with the activity of neurons that release acetylcholine

---

Antigen

-- a foreign body that induces the formation of antibodies

Antihistamine

-- a drug that interferes with the effects of histamine on cells

---

ARAS

-- the ascending reticular activating system; a brain system that mediates arousal

---

Arcuate nucleus

-- a hypothalamic nucleus that releases opiate transmitters in the limbic system

---

Area postrema

-- a specialized brain structure that lies outside the blood-brain barrier and controls the vomiting reflex

---

Astrocytes

-- specialized glial cells that comprise a part of the blood-brain barrier

---

Atropine

-- an extract from the nightshade plant (Atropos belladonna) which blocks muscarinic receptors for acetylcholine

---

Attention deficit disorder

-- a disorder that is characterized by excessive activity

Autism

-- a severe disorder that is characterized by language deficits, learning disabilities, and abnormal

responses to external stimuli

Autoimmune diseases

-- disorders that are caused by an inappropriate attack by the immune system on the body's own proteins

---

Autonomic nervous system

-- the portion of the peripheral nervous system that regulates the visceral organs, glands, and circulatory system

---

Autoreceptors

-- receptors on the presynaptic neuron that modulate activity by responding its to own neurotransmitter

---

Avoidance learning

-- a learned response to a signal that predicts the occurrence of an aversive stimulus

---

B cell

-- a specialized white blood cell that is formed in the bone marrow and participates in the humoral immune response

---

Barbiturate

-- a drug that depresses central nervous system activity

Behavioral inhibition

-- the withholding of previously rewarded responses that would now lead to nonreward or punishment

---

Behavioral pharmacology

-- the analysis of the effects of drugs on behavior

Behavioral tolerance

-- the reduced behavioral response to a drug that occurs as a result practice

---

Benzodiazepines

-- a chemical class of drugs (e.g., Librium and Valium) that typically have antianxiety effects

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Beta-lipotropin

-- a pituitary hormone incorporating several of the same sequences of amino acids that comprise peptides that are known to be important in the stress response

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Beta receptor

-- a specific receptor for epinephrine, norepinephrine, and related compounds

---

Biochemical marker

-- a specific metabolite of a neurotransmitter system that can be correlated with a specific disorder

---

Biosynthesis

-- the production of neurotransmitters by the neuron

Bipolar depression

-- a disorder that is characterized by episodes of manic behavior that are followed by severe depression

---

Blood brain barrier

-- a mechanical and lipid barrier that limits the ability of many types of molecules from reaching the neurons of the brain

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Body surface

-- includes the skin, mucous membranes, and lungs as surfaces through which drugs may enter or exit the body

---

Bright pain

-- acute, sharp pain that occurs in response to an aversive stimulus such as a pin prick

---

Caffeine

-- a naturally occurring xanthine derivative that acts as a central nervous system stimulant

---

Calcium (Ca^{++}) channels

-- membrane pores that determine Ca^{++} permeability, thereby regulating membrane excitability

---

Carbachol

-- an acetylcholine mimicker that is not inactivated by acetylcholinesterase

---

Catecholamines

-- a chemical class of compounds that includes epinephrine, norepinephrine, and dopamine

---

Cation

-- a positively charged ion (e.g., Na^{+} or Ca^{++})

Cellular response

-- an immune response that is characterized by the proliferation of T cells

---

CER

-- a conditioned emotional response, to a signal that predicts aversive consequences, which suppresses ongoing behavior

---

Cerebrospinal fluid

-- the clear filtrate of the blood that bathes and cushions the neurons of the brain and spinal cord

---

Chemical degradation

-- the inactivation of neurotransmitters (or drugs) by specific enzymes

---

Chemical transmission

-- the transfer of information from one cell to another through the release of a chemical messenger

---

Chloride (Cl^-) channels

-- membrane pores that determine Cl^- permeability, thereby regulating membrane excitability

---

Chlorpromazine

-- a drug that stabilizes the autonomic nervous system during stress and is effective in reducing psychotic symptoms, probably by blocking dopamine receptors

---

Cholinomimetics

-- a class of compounds that mimic the actions of acetylcholine

---

Choroid plexus

-- specialized blood vessels in the brain ventricles that produce cerebrospinal fluid

---

Cimetidine

-- a drug (Tagamet) used in the treatment of gastric ulcers to specifically block the H2 receptors for histamine and to reduce the release of gastric acid

---

Circadian rhythm

-- the daily cyclic fluctuations of the body's physiological systems

---

Circumventricular organs

-- a specialized group of brain structures that lie outside the blood-brain barrier allowing them to monitor changes in body conditions

---

Clinical potency

-- the typical drug dosage that therapists use to get the desired drug effect

---

Cocaine

-- a drug that can serve as a local anesthetic and a powerful central nervous system stimulant, probably through interference with the reuptake of dopamine and norepinephrine

---

Codeine

-- a narcotic drug that is one of the components of opium

Compensatory response

-- a physiological or behavioral response that opposes the direct effects of a drug or environmental stimulus

---

Competitive inhibition

-- the competition of drug molecules with the neurotransmitter molecules for access to the receptor site

---

COMT

-- an extracellular enzyme, catecholamine O-methyl transferase, that participates in the breakdown of catecholamines

---

Conditioned fear

-- the response to a signal that has been paired with an aversive stimulus

---

Conflict

-- the response to a situation in which behavior that normally has a desirable outcome may sometimes be punished

---

Contingency

-- a predictable relationship between a specific response and some change in the environment

---

Cortisol

-- a hormone released by the adrenal cortex, especially in response to stress

---

CR

-- in Pavlovian conditioning, the conditioned response to a signal that reliably predicts the occurrence of a biologically important event

---

Cross-tolerance

-- the reduced response to a drug due to exposure to some other drug

---

CS

-- in Pavlovian conditioning, the signal that reliably predicts the occurrence of a biologically important event

---

Curare

-- a drug that causes muscular paralysis by blocking the action of acetylcholine at the nerve-muscle junction

---

Cyclic AMP

-- a compound that serves as a second messenger to initiate neuromodulatory changes

---

D1 and D2 receptors

-- two receptor types for dopamine

DBH model

-- Stein and Wise's biological model that proposes reduced dopamine beta hydroxylase as a possible cause of schizophrenia

---

Delay conditioning

-- in Pavlovian conditioning, a procedure in which a signal is accompanied, after a brief delay, by a biologically important event

---

Delirium tremens

-- a progressive dysfunction of the motor system that occurs in response to long-term alcohol consumption

---

Delta wave

-- the characteristic slow-wave EEG pattern that accompanies periods of deep sleep

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Denervation supersensitivity

-- an exaggerated sensitivity of neurons to a neurotransmitter following the destruction of presynaptic neurons

---

2-deoxy glucose

-- a compound (similar to glucose) that can be radioactively labeled to assess the metabolic activity of different brain areas

---

Depolarize

-- to reduce the electrical potential across the membrane of the neuron

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Dexamethasone suppression test

-- a measurement of the ability of dexamethasone (a synthetic cortisol) to suppress cortisol production which has been useful in the diagnosis of depression

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DHPG

-- a metabolite (3,4-dihydroxyphenethylene glycol) of catecholamines that may serve as a biochemical marker for certain types of depression

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Diffusion

-- the random movement of ions or other particles toward a uniform distribution or concentration (e.g., across the neuronal membrane)

Digitalis

-- an extract from the foxglove plant (Digitalis purpura) which acts as an autonomic nervous system stimulant

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Disulfiram

-- a drug that interferes with the enzyme acetaldehyde dehydrogenase, thus causing illness following alcohol ingestion

---

Dopamine

-- one of the catecholamines, a neurotransmitter of the central nervous system, and a hormone of the adrenal medulla

---

Dose-response curve

-- the relationship between different dosages of a drug and the accompanying changes in physiology or behavior

---

Drug

-- a chemical compound (natural or synthetic) that is administered for its specific effects

---

Drug action

-- the biochemical effect of a drug on the neuron, especially at the synapse

---

Drug effect

-- the end result of a drug's action that is reflected by a change in physiology or behavior

---

Dull pain

-- the long-term, throbbing sensation of pain

Dynamic synapse

-- the concept of the synapse as a system that undergoes constant change through the regulation of transmitter release, number of receptors, and so forth

---

E

-- (see Epinephrine)

ED-50

-- the amount of drug that serves as an effective dose for 50 percent of the population

---

Electroconvulsive therapy

-- a procedure, frequently used in the treatment of depression, that involves the passage of electric current through the brain to induce seizure activity

---

Emergence

-- the appearance of specific behavioral abilities in concert with the maturation of specific brain systems

---

Encephalization

-- the pattern of brain maturation from lower to progressively higher regions

---

Endorphins

-- the term applied to a group of endogenous peptides that are involved in pain reduction

---

Enkephalins

-- the term applied to the two small peptides that were the first morphine-like substances discovered in animals

---

Enzyme induction

-- the increased production of an enzyme that occurs as a result of exposure to the substrate

---

Ephedrine

-- a drug that acts indirectly by causing the release of norepinephrine from the neuron

---

Epinephrine

-- one of the catecholamines, the principle hormone of the adrenal medulla that is released during certain types of stress; also known as adrenaline

---

Ergot

-- a grain fungus that is a stimulant of the sympathetic nervous system

---

Escape learning

-- the acquisition of a response that terminates an aversive stimulus

---

Experimental extinction

-- in Pavlovian conditioning, the repeated presentation of a CS that had previously signaled a biologically important event (the US)

Extrapyramidal motor system

-- one of the systems of the brain responsible for body movement

---

False transmitter (+/-)

-- a substance that can be stored in a neuron and released by neural activity; the compound may enhance (+) or interfere with (-) normal neurotransmitter activity

---

Flight-or-fight response

-- a sympathetic nervous system response that prepares an organism to cope with a stressful event

---

Flinch/jump test

-- a procedure to measure the pain threshold

Free operant (Sidman) avoidance

-- an unsignaled avoidance training procedure in which each response postpones the delivery of the next shock

---

GABA

-- an inhibitory neurotransmitter (gamma amino butyric acid) that is abundant throughout the brain

---

GABA receptor complex

-- a receptor structure with separate sites for GABA, sedative/convulsants, and benzodiazepines that regulates Cl^- channels

---

Ganglionic stimulation

-- the excitation of the autonomic nervous system ganglia via chemical or electrical stimulation

---

General adaptation syndrome

-- the sequence of physiological responses to stress as described by Hans Selye

---

Generalized fear

-- the spreading of a conditioned fear response from the initial, specific CS to other situations

---

Glycine

-- an amino acid that is also a neurotransmitter (usually inhibitory) in the spinal cord and brain

---

H1 receptor

-- a type of histamine receptor that mediates responses to injury or allergies throughout the body

---

H2 receptor

-- a type of histamine receptor that mediates the release of gastric acid from the stomach

---

Half-life

-- the amount of time required for half of the drug dosage to be inactivated or removed from the body

---

Haloperidol

-- a drug that blocks dopamine (D2) receptors and is commonly used in the treatment of schizophrenia

---

Heroin

-- a synthetic opiate drug

5-HIAA

-- a metabolite (5-hydroxy indole acetic acid) of serotonin that may serve as a biochemical marker in the diagnosis of suicidal depression

---

Hippocampal theta

-- a characteristic EEG pattern in the septohippocampal system that appears to be mediated by cholinergic neurons

---

Histamine

-- an amine compound that is present throughout the body, participating in responses to injury and immunological challenges

---

Hormones

-- naturally occurring compounds, released into the bloodstream by endocrine glands, that stimulate chemically specific receptors on target organs

---

Humoral response

-- an immune response that involves the production and release of specific antibodies by the B cells

---

HVA

-- a metabolite (homovanillic acid) of dopamine that may serve as a biochemical marker in the diagnosis of certain types of schizophrenia

---

Hyperkinesis

-- (see Attention deficit disorder)

Hypodermic syringe

-- a device for injecting drugs under the skin

Immunoglobulins

-- a set of five different types of antibodies, produced by B cells, which are probably involved in separate types of humoral immune responses

---

Inactivation

-- the rapid termination of the activity of a neurotransmitter to allow the postsynaptic cell to recover and be ready to initiate the next action potential

---

Indirect action

-- the action of drugs that have little or no effect on the postsynaptic receptors, but produce their effects by stimulating the release of the normal neurotransmitter

---

Inhalation procedure

-- the administration of drugs through the membrane surfaces of the lungs

---

Interstitial fluid

-- the extracellular fluid that bathes cells throughout the body

---

Intraarterial administration

-- the administration of a drug by injection directly into an artery

---

Intracerebral administration

-- the administration of a drug by injection or application directly into brain tissue

---

Intracisternal administration

-- the administration of a drug by injection directly into the cerebrospinal fluid

---

Intracranial administration

-- the administration of a drug locally into the brain, usually by the Intra cerebral or Intra cisternal route

---

Intramuscular administration

-- the administration of a drug by injection directly into a muscle

---

Intraperitoneal administration

-- the administration of a drug by injection through the abdominal wall into the space surrounding the viscera

---

Intrathecal administration

-- the administration of a drug (typically an anesthetic) by injection through the spinal sheath into the local region surrounding the spinal cord

---

Intravenous administration

-- the administration of a drug by injection directly into an vein

---

Iproniazid

-- a drug that inhibits the activity of the enzyme monoamine oxidase and is commonly used in the treatment of depression

---

Ischemia

-- the loss of blood (and oxygen) supply to an organ or portion of an organ

---

James-Lange theory

-- the theory that the expression of an emotion occurs before the experience of an emotion

---

L-DOPA

-- a precursor of dopamine and norepinephrine

Law of initial values

-- the principle that a drug effect depends on the initial level of the physiological or behavioral system

---

LD-50

-- the dosage of a drug that would be lethal to 50 percent of the population

---

Learned helplessness

-- the result, generalized to other situations, of learning that one's behavior is ineffective in changing the environment

---

Leukocytes

-- white blood cells that commonly participate in the body's response to injury or immunological challenges

---

Limbic system

-- a set of brain structures involved in emotional and motivational responses

---

Lipid soluble

-- the ability of a relatively large molecule to enter a cell by dissolving in the lipid (fat) membrane of the cell

---

Lithium

-- a simple salt that is commonly used in the treatment of manic behavior

---

Liver enzymes

-- in this context, enzymes formed by the liver that facilitate the breakdown of drugs

---

Locus coeruleus

-- the primary location of neurons that send axons through the MFB to release norepinephrine in the anterior cortex

---

Long delay conditioning

-- in Pavlovian conditioning, a procedure in which the CS is presented for a relatively long period of time before being accompanied by the US

LSD

-- a drug (lysergic acid diethylamide) that causes various forms of hallucinations

---

Lymphokines

-- compounds released by sensitized T cells in the cellular immune response

---

Macrophage

-- specialized white blood cells that engulf potential antigens and "present" them to B cells

---

MAO

-- an intracellular enzyme (monoamine oxidase) that converts catecholamines and serotonin into inactive forms

---

MAO inhibitor

-- a drug that inhibits the activity of MAO, allowing neurotransmitter levels to increase; commonly used in the treatment of depression

---

MAO isozymes

-- different forms of MAO that are present throughout the body (MAO-A) and in the brain (MAO-B)

Mast cells

-- large cells in connective tissues, respiratory tract, eyes, and lymph glands that participate in the humoral immune response

---

Mecholyl

-- a drug that mimics acetylcholine at muscarinic receptor sites

---

MED-50

-- minimum effective dose for 50 percent of the population

Melatonin

-- a hormone, released by the pineal gland, that participates in circadian rhythms

---

Membrane pores

-- interruptions in the cell membrane that allow small molecules to enter and exit the cell

---

Methyl atropine

-- a positively charged form of atropine that does not cross the blood-brain barrier

---

Methyl scopolamine

-- a positively charged form of scopolamine that does not cross the blood-brain barrier

---

MFB

-- a collection of fibers (the medial forebrain bundle) that projects through the hypothalamus to the anterior cortex and participates in the reward system

---

MHC

-- the template (major histocompatibility complex) in T cells that is used to determine self versus non-self

---

MHPG

-- a metabolite (3-methoxy-4 hydroxyphenylethylene glycol) of dopamine and norepinephrine that may be a biochemical marker for the diagnosis of depression

---

Mitogen

-- a compound that facilitates the proliferation of T cells

Morphine

-- a narcotic drug that is one of the components of opium

Mucous membranes

-- the smooth membranes lining the nose and mouth; some drugs can be readily administered through these membranes

---

Muscarine

-- a drug (derived from the mushroom Amanita muscaria) which mimics acetylcholine in the parasympathetic and central nervous systems

---

Muscarinic receptors

-- specific acetylcholine receptors (defined by their response to muscarine) that are present in the parasympathetic organs and in the central nervous system

---

Myasthenia gravis

-- a grave weakening of the muscles caused by a decrease in the acetylcholine receptors of the somatic muscles

---

Naloxone

-- a drug that blocks opiate receptor sites

Narcotic

-- a drug that causes a numbing of pain and other sensations

Negative afterimage

-- a perceptual illusion (usually of the visual system) which follows the termination of a strong stimulus

---

Nerve-Muscle junction

-- the region where alpha motor neurons release acetylcholine onto receptors in the muscles

---

Neurochemistry

-- the analysis of the response of neurons to drugs

Neuromodulation

-- relatively long-term changes in neuronal function (e.g., increase in transmitter or decrease in receptors) that occur in response to drugs, behavioral experience or other influences

---

Neuron doctrine

-- the notion that the brain is comprised of individual cells rather than a syncytium of protoplasm

---

Neuronal specificity

-- the similarity among brains in terms of anatomical pathways, neurochemistry, and other features of organization

---

Neurotoxin

-- a compound that leads to the impairment or destruction of neurons

---

Neurotransmitter

-- a compound that is stored in the terminal endings of neurons, released into the synapse by the arrival of an action potential, and bound with a specific receptor

---

Nicotine

-- a compound (present in tobacco) that mimics acetylcholine at receptors in the autonomic nervous system, the central nervous system, and the somatic muscles

---

Nicotinic receptors

-- specific acetylcholine receptors (defined by their response to nicotine) that are present in the autonomic ganglia, the somatic muscles, and at some central nervous system sites

---

Nigrostriatal pathway

-- fibers from cells of the substantia nigra that project to dopamine receptors in the striatum and comprise a major pathway of the extrapyramidal motor system

---

Noncompetitive inhibition

-- the antagonistic effect of drugs that alter the shape or structure of a receptor rather than mimicking a neurotransmitter

---

Nonspecific anxiety

-- a generalized feeling of fear or anxiety for which no specific cause can be identified by the individual

---

Norepinephrine

-- one of the catecholamines, a neurotransmitter of the sympathetic and central nervous systems, and a hormone of the adrenal medulla

---

6-OHDA

-- a neurotoxin (6-hydroxy dopamine) that destroys the terminal endings of cells that release dopamine or norepinephrine

---

Operant behavior

-- B. F. Skinner's descriptive and empirical system of the analysis of instrumental behavior

---

Opioid link

-- a short neuron in the spinal cord that relays pain inhibitory messages from descending serotonergic fibers by releasing opioid neurotransmitters that block incoming pain signals

---

Opium

-- a narcotic compound (derived from the opium poppy), that is comprised of morphine and codeine

---

Opponent process theory

-- Solomon and Corbit's theory that the termination of a situation that elicits a strong emotion will elicit an opponent emotion

---

Oral administration

-- the administration of drugs by ingestion through the mouth

---

Organismic variables

-- age, sex, body weight, and so forth can influence the size or direction of a drug effect

---

Parasympathetic

-- the division of the autonomic nervous system that is involved with vegetative processes; postganglionic fibers release acetylcholine

---

Parkinsonism

-- a progressive dysfunction of dopamine fibers in the extrapyramidal motor system

---

Pavlovian conditioning

-- the procedures, originally described by Pavlov, that allow the learning of relationships among environmental stimuli

---

Paw-lick test

-- a procedure to measure the pain threshold

PEA

-- an amphetamine-like compound that may serve as a biochemical marker in the diagnosis of certain types of schizophrenia

---

Pentylenetetrazol

-- a convulsant drug (Metrazol) that stimulates the nervous system by reducing the recovery time between action potentials

---

Peptides

-- short chains of amino acids, some of which serve as neurotransmitters

---

Periaqueductal gray

-- a collection of cell bodies in the brain stem that plays an important role in pain reduction

---

Pharmacological tolerance

-- physiological adjustments that reduce a drug's action following repeated exposures to the drug

---

Phenothiazines

-- a chemical class of drugs that is commonly used in the treatment of psychotic symptoms

---

Phencyclidine

-- a hallucinogen (PCP) that interferes with several different transmitter systems

---

Phenylketonuria

-- a disorder caused by the genetic absence of a single enzyme that disrupts the development of serotonergic neurons (among others)

Phosphoinositide cycle

-- a second messenger system that initiates neuromodulatory changes

---

Physical dependence

-- a drug-induced change in the body's physiology that necessitates the presence of the drug for normal function

---

Picrotoxin

-- a stimulant drug that acts on the GABA receptor complex to reduce Cl^- permeability

---

Pineal gland

-- a brain structure that plays an important role in circadian rhythms

---

Pituitary

-- the master gland of the neuroendocrine system

Placebo

-- an inactive compound that may have an effect when it is administered as though it were a specific drug

---

Plasma compartment

-- the fluid portion of the blood

Pools

-- any of several locations (e.g., bladder or fat deposits) where a drug may be present in the body while having no effect

---

Postsynaptic neuron

-- the neuron that receives chemical messages from other neurons

---

Postsynaptic inhibition

-- the interference with chemical transmission by blocking or changing the shape of the receptors for the neurotransmitter

---

Pre-post design

-- a procedure for discriminating behavioral tolerance from pharmacological tolerance

---

Precursor

-- a compound that can be readily transformed into an active substance by the body

---

Preformed chemical mediators

-- a collection of compounds released by sensitized mast cells in the hay fever reaction

---

Presynaptic neuron

-- the neuron that sends messages to other neurons

Presynaptic inhibition

-- the interference with chemical transmission by blocking the action potential or the release of the neurotransmitter

---

Primary symptoms

-- the symptoms that are always present in a disorder and are useful in establishing a diagnosis

Proliferation

-- the rapid increase in the number of sensitized T cells during the cellular immune response

Protein binding

-- the attachment of a drug molecule to a large protein molecule which effectively inactivates the drug

Psychopharmacology

-- an analysis of the effects of drugs on mood, emotions, and other aspects of human behavior

Punishment

-- aversive events that are contingent upon the occurrence of a specific response

Raphe nucleus

-- a collection of serotonergic neurons in the brain stem that is involved in sleep

Rate-limiting enzyme

-- the enzyme that mediates the slowest step in a series of chemical reactions

Rebound effects

-- the behavioral effects, opposite to those produced by a drug, that occur when the drug is abruptly withdrawn

Receptor antibodies

-- substances produced by the immune system that destroy the body's own receptors

Receptor binding

-- the attachment of a drug to a receptor site; this drug/receptor complex can be isolated for study

---

Receptor sites

-- specific protein structures in the cell membrane that match the structure of the neurotransmitter molecule

---

Rectal administration

-- the administration of drugs through the membrane surfaces of the colon

---

Recurrent inhibition

-- a feedback loop in which the activity of a neuron inhibits further activity

---

REM sleep

-- a portion of the sleep cycle that is characterized by rapid eye movement, behavioral sleep, an "alert" EEG pattern, and dream reports

---

Renal excretion

-- the removal of a drug from the body through the action of the kidneys

---

Renshaw cell

-- a small neuron in the spinal cord that receives cholinergic input from motor nerves and releases glycine to produce recurrent inhibition

---

Reserpine

-- a drug which causes the gradual depletion of catecholamines and serotonin from neurons

---

Resting potential

-- the membrane potential (-70 millivolts inside) of an inactive neuron

---

Reticular formation

-- a diffuse net of small neurons in the brain stem that participates in the ascending arousal system

---

Reuptake

-- the inactivation of a neurotransmitter by transporting it back into the neuron that released it

---

Reward system

-- the brain structures (including the MFB, limbic system, and anterior cortex) that release catecholamines and mediate rewarded behavior

---

Ritualistic behavior

-- a regimen associated with the self-administration of a drug

---

Schizoaffective disorders

-- mental illnesses that are characterized by some of the same symptoms as schizophrenia

---

Schizophrenia

-- a severe psychotic disorder characterized by disordered thought processes, flattened affect, and withdrawal; usually associated with dopamine dysfunction

---

Scopolamine

-- a drug that blocks acetylcholine receptors in the parasympathetic and central nervous systems

---

Second messengers

-- compounds that initiate changes in neuronal function following the arrival of the neurotransmitter ("first" messenger)

Secondary reinforcer

-- a previously neutral stimulus that has rewarding properties as a result of its association with rewarding stimuli

---

Secondary symptoms

-- symptoms that may sometimes be present in a disorder, but are not consistent enough to be used for diagnosis

---

Self-administration

-- the voluntary administration of drugs that have rewarding properties

---

Semipermeable membranes

-- cell membranes having pores that allow small particles to pass through but restrict the passage of larger particles

---

Senescence

-- the stage of late adulthood

Sensitization

-- an exaggerated response to a drug because of prior exposure to that drug

---

Septohippocampal system

-- the local neuronal circuits between the septum and the hippocampus which release acetylcholine in the regulation of the hippocampal theta rhythm

---

Serotonin

-- a compound (5-hydroxytryptamine) that is common throughout the body, and also serves as a neurotransmitter in the central nervous system

---

Side effects

-- any unintended effect of a drug

Social defeat

-- a procedure to produce the experience of submission which can lead to neurochemical changes associated with the stress response

---

Sodium (Na^+) channels

-- membrane pores along the axon which open to increase Na^+ permeability during the propagation of the action potential

---

Sodium pump

-- an active transport system that regulates the resting potential by maintaining the high extracellular concentration of Na^+

Spontaneous remission

-- the recovery from a disorder (e.g., depression) in the absence of treatment

---

Stage of alarm

-- the first stage of Selye's general adaptation syndrome, which initiates responses to the stressor

---

Stage of exhaustion

-- the final stage of Selye's general adaptation syndrome in which the organism's ability to counteract the stressor is depleted

---

Stage of resistance

-- the second stage of Selye's general adaptation syndrome in which the organism's physiological systems are actively combating the stressor

---

Storage pools

-- the regions within a neuron where neurotransmitter molecules are stored before becoming available for release

---

Structure-activity relationship

-- the correlation between chemical structure and drug effects

---

Strychnine

-- a stimulant drug that acts primarily by blocking the inhibitory effects of glycine receptors

---

Subcutaneous administration

-- the administration of drugs by injection under the skin

Substance abuse

-- the use of a drug or some other substance to an extent which interferes with work or family environments

---

Substance P

-- a peptide neurotransmitter that is released in the spinal cord by incoming pain fibers

---

Substantia nigra

-- a group of dopamine neurons that project to D2 receptors in the extrapyramidal motor system

---

Subtractive model

-- a method of analyzing structure/function relationships by determining which function is no longer present following the removal of a specific brain structure

---

Sudden death

-- death resulting from massive parasympathetic discharge that can be triggered by an acute stressor for which there is no obvious coping response

---

Suprachiasmatic nucleus

-- a structure of the hypothalamus that participates in circadian rhythms

---

Surgical shock

-- a generalized stress syndrome associated with surgical procedures

---

Sympathetic

-- the division of the autonomic nervous system that is involved with arousal processes; postganglionic fibers release norepinephrine

---

Sympathomimetic

-- drugs that mimic or otherwise increase the activity of neurotransmitters associated with the

sympathetic nervous system

Synapse

-- the gap between successive neurons where chemical transmission takes place

---

Synaptic vesicle

-- small packets in the terminal endings of neurons where neurotransmitter molecules are stored for release

---

Syncytium

-- Golgi's notion that the nervous system was comprised of an interconnected net of protoplasm

---

T cell

-- a specialized white blood cell that is formed in the thymus gland and participates in the cellular immune response

---

Tachyphylaxis

-- rapid tolerance to the indirect actions of drugs

Tail-flick test

-- a test to determine the pain threshold

Tardive dyskinesia

-- an impairment of extrapyramidal motor system functions that eventually appears as a side effect of phenothiazines

---

Target organ

-- organs that have specific receptor sites for circulating hormones

---

Terminal endings

-- the final portion of the neuron that contains the mechanisms for the release of the neurotransmitter

---

Tetanus toxin

-- a substance that blocks the release of acetylcholine from alpha motor neurons

---

Tetrabenazine

-- a synthetic tranquilizer that produces effects similar to those of reserpine

---

Theobromine

-- a naturally occurring xanthine derivative that acts as a central nervous system stimulant

---

Theophylline

-- a naturally occurring xanthine derivative that acts as a central nervous system stimulant

---

Therapeutic ratio

-- the ratio of LD-50 to MED-50 that represents the clinical safety factor of a drug

---

Theta wave

-- a regular EEG pattern that accompanies the early stages of falling asleep

---

Think-drink effect

-- the observation that behavior is more closely related to perceived alcohol consumption than to actual consumption

---

Tolerance

-- a reduced response to a drug following repeated exposures to the drug

---

Trace conditioning

-- in Pavlovian conditioning, a procedure in which the CS is terminated for a brief period before the US is presented

---

Transdermal administration

-- the administration of a drug by application to the skin surface

---

Transpleural administration

-- the administration of a drug by injection into the space surrounding the lungs

---

Triad design

-- a procedure that involves the simultaneous testing of three groups: an untreated group, an experimental group, and a yoked control group

---

Tricyclic antidepressants

-- a chemical class of compounds that block the reuptake of catecholamines and are used in the treatment of depression

---

Two factor theory

-- the theory that avoidance behavior is based on a combination of Pavlovian and instrumental conditioning

---

Two way avoidance

-- an avoidance training procedure in which the signaled shock is presented alternately in either end of a shuttle box

---

Tyramine

-- a dietary amino acid; causes the "wine and cheese" effect during treatment with MAO inhibitors

---

Tyrosine hydroxylase

-- the rate-limiting enzyme in the synthesis of catecholamines

---

Ulcers

-- stomach lesions caused by excessive parasympathetic activity due to stress

---

UR

-- in Pavlovian conditioning, the reflexive response that is elicited by a biologically important event (the US)

US

-- in Pavlovian conditioning, a biologically important event (e.g., food powder or electric shock) that elicits a reflex (the UR)

Vagusstoff

-- Loewi's term for the chemical (acetylcholine) released by electrical stimulation of the vagus nerve

---

Vehicle

-- the carrier (usually a solution) mixed with the drug in order to facilitate its administration

---

Ventral tegmental area

-- a collection of neurons in the region of the pons that project axons through the MFB and release dopamine in the limbic system and anterior cortex

---

Withdrawal effects

-- symptoms (usually aversive) that accompany the abrupt cessation of drug use

---

Xanthines

-- a group of stimulant compounds (including caffeine, theobromine, and theophylline) that occur naturally in coffee, tea, chocolate and cola and act by increasing Ca^{++} permeability

---

Yerkes-Dodsen law

-- the inverted U-shaped relationship between arousal and performance

---

Yoked control

-- a procedure in which the environmental consequences for one subject are linked to the behavior of another subject

---

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The autonomic nervous system uses a combination of different anatomical organizations and different chemical mediators to cause different (usually opposing) effects in the same target organs.

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Subtractive logic as it applies to lesion and pharmacological experiments.

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Subtractive logic as it applies to the famous case of Phinnaeus P. Gage.

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Subtractive logic as it applies to the metabolic disorder of phenylketonuria (PKU).

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Three types of Pavlovian conditioning procedures for modeling of fear: Delay conditioning. Conditioned responses, including fear, begin to occur during the CS presentation before the US is presented. Long-delay conditioning. Conditioned fear responses move forward in time during long CS presentations and, with continued training, reach maximal levels during the interval just preceding the presentation of the aversive US. Trace conditioning. Conditioned fear can be observed during the interval when only the trace, or memory, of the CS is present.

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The effects of either morphine, placebo drugs, or acupuncture on dental pain can be blocked by an opiate blocker.

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