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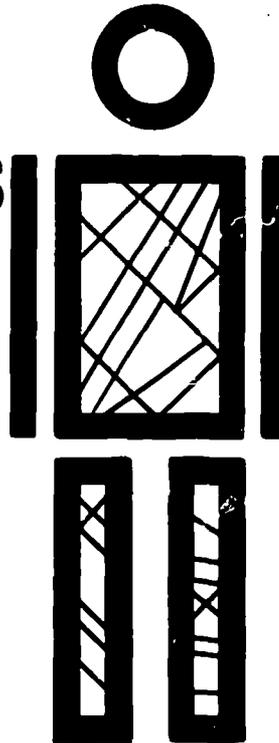
ABSTRACT

Designed for use in biology classes at the senior high school level, this informational booklet can serve as a resource in an interdisciplinary drug abuse education program. Its purpose is to assist the teacher who wishes to supplement the regular program with instruction in the effects of drugs on body systems by providing materials to be used at the discretion of the teacher as it fits into his planned program. Topics include: (1) a general description of frequently abused drugs, (2) effects of drugs on cells, (3) skeletal muscle and drug use, (4) circulatory aspects of drug use, (5) metabolic aspects of drug use, (6) excretory aspects of drug use, (7) the nervous system and drugs, (8) effects of drugs on homeostatic mechanisms, (9) the endocrine system and drugs, (10) gastrointestinal aspects of drug use, and (11) genetic aspects of drug use. A bibliography is appended. (BL)

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EFFECTS OF DRUGS ON BODY SYSTEMS



DIVISION OF INSTRUCTION • DADE COUNTY PUBLIC SCHOOLS, MIAMI, FLORIDA

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**EFFECTS OF DRUGS ON
BODY SYSTEMS**

Instructional Publication No. 4-8F

1970 Edition

**Third Printing
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Dade County Public Schools
Miami, Florida**

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PREFACE

This publication was designed for use in biology classes at the senior high school level. Its purpose is to assist the teacher who wishes to supplement the regular program with instruction in the effects of drugs on body systems by providing material to be used at the discretion of the teacher as it fits into his planned program. While this chiefly a biology supplement, it could be utilized by senior high school science teachers in any of their classes.

The publication is not intended to serve as an entire drug abuse education program. Other resources, such as outside speakers and various educational media in the form of handbooks, brochures, and film, will contribute to a meaningful program.

The total program on drug and substance abuse should be schoolwide--an interdisciplinary undertaking, planned with the cooperation of persons in the various subject areas, guidance, and administration.

In addition to this publication, the following Dade County instructional publications in the same area are available:

Drug Abuse Education in the Elementary School, 4D (a teacher guide)

Narcotics and Dangerous Drugs, Student Handbook, Elementary School, 4G-1

Drug Abuse Education in the Junior High School, 4E (a teacher guide)

Drugs and You, Student Handbook, Junior High School, 4G-2

Drug Abuse Education in the Senior High School, 4F (a teacher Guide)

Senior High School Student Handbook for Drug and Substance Abuse Education, 4F-CP-1A (Revision will be 4G-3)

Eleven Lessons in Drug Abuse Education for Use in Junior High School Science, 4-8A (a teacher guide)

Lessons in Drug Abuse Education for Independent Study (elementary and junior high) Teacher Edition, 4D-SU-1T; Student Edition, 4D-SU-1S

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A GENERAL DESCRIPTION OF FREQUENTLY ABUSED DRUGS

Narcotics

Narcotics are defined as drugs which produce stupor or insensibility due to their depressant effect on the central nervous system. Examples of narcotics that are known to be in common abuse are opium and its derivatives, morphine, codeine, heroin and paregoric.

Opium is taken from the poppy *Papaver somniferum*. It is the unripened green seed capsule that provides the opium after a long and tedious process--one that limits its production to only those countries where labor is cheap. It was introduced to the United States by Chinese immigrants. The chief sources of opium are India, Persia, Turkey, Yugoslavia, Macedonia, Bulgaria, and China. From crude opium are derived some twenty-five different alkaloids, among them morphine and codeine. Heroin is derived from morphine by a relatively simple process.

Dr. Lawrence Kalb, one of the world's leading authorities on opiates (as the derivatives of opium are called), says that the intensity of pleasure produced by opiates is in direct relation to the degree of psychopathy. This observation has the support of many of this country's experts on narcotics. The consensus among those who are informed about narcotics is that people of normal mentality derive little or no pleasure from the use of these drugs. In fact, it has been shown experimentally that many individuals who were given opiates actually considered the experience unpleasant.

The opiates can produce the feeling of well-being, physical comfort, and sleep in those who are the victims of serious accidents and painful disease. It is in this capacity that the opiates--morphine in particular--have their greatest value. Morphine is the world's most widely used

reliever of acute pain. It is named after Morpheus, the god of dreams.

When taken in large, prolonged doses, the narcotics produce physical dependence on the part of the user. When the chronic user attempts to terminate the taking of narcotics, he experiences the horror of the physical dependence syndrome.

Codeine, like morphine, has been known since antiquity. It is a less effective analgesic that is one of the alkaloids found in the poppy plant. Its use in medicine is mostly limited to cough medicines.

Heroin was isolated in the 1890's by heating morphine with acetic acid. It proved to be a superior analgesic, but its habituating ability was found to be so great as to offset its value as a pain reliever. Even so, it is the most popular opiate on the illegal market, but it is not used nearly so extensively in medicine as morphine and codeine.

Some success in the treatment of heroin addicts with a synthetic drug called methadone has been reported. Methadone was developed as a substitute for morphine by the Germans in World War II. Used among addicts, it has the effect of eliminating their craving for heroin and allowing them to lead reasonably normal lives. Eventually an attempt is made to completely remove the addict from the drug habit. Several cities claim success with the methadone treatment. The drug is also inexpensive, costing only about ten cents a day. It has not been proven that this is an entirely successful means of treating heroin addicts or that it will not create methadone addicts.

Paregoric, because it is relatively easy to obtain, is sometimes used by addicts as an alternative to stronger, less obtainable drugs. Doctors prescribe it as a remedy for infantile colic and diarrhea.

A major advance in the use (and abuse) of narcotics came with the invention of the hypodermic syringe. The narcotics lend themselves nicely to the use of this device, and their effects are enhanced when they are injected directly into the blood. Before this time, the opiates were smoked or eaten, and some of their effectiveness was lost.

Psychotomimetic Drugs

By definition, psychotomimetic drugs are compounds which provide distortions of perception, dream images, and hallucinations. The most commonly abused of these drugs are LSD, mescaline, psilocybin, and Cannabis.

Originally, LSD was studied as a possible key to nerve cell chemistry. The LSD molecule--technically, lysergic acid diethylamide--contains a part that resembles serotonin. Serotonin appears to function in the transmission of impulses across synapses. One theory of LSD function holds that this similarity in structure enables the drug molecule to trick neurons into accepting it as serotonin. In this way, the impulses are transmitted in an altered form; thus may be created the illusions and bizarre behavior so characteristic of the LSD trip.

Lysergic acid diethylamide was first synthesized by a Swiss scientist named Hoffman while working with a rye-infecting fungus called ergot. Hoffman accidentally ingested LSD and unintentionally took the first LSD trip.

The effects of LSD resemble those of schizophrenia. Indeed, schizophrenics often have a high resistance to LSD. This and the presence of certain chemical structures--indoles--in the brains of schizophrenics and in LSD may mean that the similarity between the LSD trip and Schizophrenia may be more than coincidental.

Users of LSD do not always lose the effects of its use quickly. Occasionally reoccurrences of the symptoms of LSD use can take place without the taking of additional doses, and cases of insanity have been reported as being a direct result of LSD use. The user of LSD develops a tolerance very quickly.

Mescaline is derived from the peyote cactus, one of the magic plants of Mexico. It was isolated more than seventy years ago by the chemist Heffter. Mescaline was first used by Indian tribes of Mexico and the southwestern United States. Chemically it bears a resemblance to the hormone epinephrine and the neurohormone norepinephrine. Its effects are similar to those of LSD but considerably less intense.

Psilocybin is obtained in a colorless crystalline form, is highly stable, and dissolves readily in water. As a hallucinogen, it is similar to LSD but not as potent. It is isolated from a Mexican mushroom and was used by primitive tribes in religious rites.

Cannabis is described in the writings of the Chinese as much as 5,000 years ago. The psychotomimetic agent is contained in the resins produced by the tops of the female plant. The male of this dioecious species produces the same resins, but in small, difficult-to-obtain quantities.

Surprisingly little is known about the pharmacological aspects of Cannabis. Presently the psychotomimetic properties of the plant are under intensive study. It is anticipated that the results of this research will reveal a great deal concerning the nature of the plant and will place concerned individuals in a better position to answer questions about its effects. This much is known about Cannabis: it is a true and potent hallucinogen with little or no medical value. The questions yet to be answered

relate to its permanent and harmful effects.

Depressants

This group of drugs includes the barbiturates and tranquilizers. They are named for their depressing effect on the central nervous system. Their abuse is limited mostly to those of low socio-economic standing and to individuals who can face life only if it is dulled by depressants. The numbing effects of tranquilizers and barbiturates are not considered to be desirable by the most drug addicts and for this reason they are not as seriously abused as the stimulants and narcotics.

Barbiturates (also known as soporifics because of their sleep-inducing qualities) seem to act on the cortex of the brain. Since this is the thinking and environment analysis center of the brain, these faculties are the most obviously affected by the use of barbiturates. In hypertensive persons, they produce a lack of anxiety and pressure that is pleasing. They are habituating in all chronic users, and withdrawal from their use is said to present a serious medical situation that can result in convulsions and death.

Pentobarbital, phenobarbital, amobarbital, and secobarbital are barbiturates all of which have proven to be useful in medicine and psychotherapy. They are all related to the compound barbitol.

Tranquilizers are depressants of a less potent nature. Two of these--chlorpromazine and reserpine--resemble LSD in their chemical structure but are entirely different in their effects on the central nervous system. Both appear to reduce the supply of neurohormones that are necessary for impulse transfer. Particularly affected by tranquilizers are the hypotha-

lamus and that part of the brain which controls many emotional reactions.

Chronic users develop a tolerance to tranquilizers and must continually increase their daily doses in order to obtain the desired effect. These drugs are habituating to the extent that, when the addict attempts to withdraw from their use, he experiences extreme physical discomfort characterized by headaches and nausea.

Tranquilizers are usually obtained illegally with falsified prescriptions or through individuals who have legal access to them. Because they depress consciousness and alertness, they are not as sought after as drugs that have the opposite effect.

Stimulants

From the pharmacologist's standpoint, stimulants are compounds that quantitatively increase the functioning of a cell, tissue, or organ. Examples of commonly abused stimulants are the amphetamines (dexedrine and benzedrine), cocaine, and caffeine.

Amphetamines have been used with considerable success in the treatment of minor neurotic depression. In recent years, it has become popular as an appetite suppressor for overweight people.

The effects of amphetamine are as varied as they are complex. Its mode of action appears to involve the release of neurohormones, which in turn increase the responsiveness and activity of the central nervous system. Most experts agree that there is, at present, no completely acceptable explanation of amphetamine function. The postdepressive phase of amphetamine use also is not adequately explained. Some say that amphetamine use after a time results in a depletion of the brain's neurohormones that decreases the brain's activities.

The Indians of South America have been chewing the leaves of the coca shrub for the stimulating effects of its cocaine since long before the coming of the Spanish Conquistadores. It has been estimated that more than 90 percent of the poverty-stricken Andean Indians habitually chew coca leaves to relieve the agony of hunger.

In the United States, cocaine is used by addicts in a white, powdery form--"snow." It creates for the addict a feeling of euphoria and excitement that is followed by a period of depression similar to that experienced by amphetamine users.

Chemically, caffeine belongs to a group of compounds known as purines. Experimentally, it has been shown that it has a stimulating effect on the cerebral cortex. A component of coffee, tea, and cola drinks, caffeine is consumed in enormous quantities by the people, generally the adults, of the United States. Usually, however, the amount taken at any one time is so small that its effects are hardly discernable except when they come in the form of a sleepless night after the drinking of several cups of coffee.

It is when the drug is used in concentrated doses that it becomes dangerous as well as habituating. It is the least abused of the stimulants, probably because it is relatively unavailable in concentrated form.

The amphetamines are unique among central nervous system stimulants in that they have enormous potential for tolerance induction. Tolerance develops slowly but may eventually lead to the user's ingesting several hundred times the original dosage. These large doses are occasionally fatal and at least cause pronounced behavioral changes, including hallucinations and delusions.

Some of the stimulants (or sympathomimetics, as they are sometimes known) are powerful vasoconstrictors and are used in nose sprays to treat

swollen membranes caused by allergies. Other effects brought about by sympathomimetics are bronchodilation in victims of bronchial asthma and the removal of allergic symptoms. Modern chemistry has developed a wide range of tailor-made sympathomimetics that have only the desired effect on a specific problem with none of the side effects.

Alcohol

Alcohol is the most widely used of the drugs. Its use is recorded in the oldest writings of man. Americans consume 212,245,000 gallons of alcohol each year. This is the equivalent of thirty-six pints of 100 proof whiskey for every person over the age of sixteen.

The principal type of alcohol in beverages is ethyl alcohol. Another type of alcohol--methyl, or wood, alcohol--is also used occasionally. Methyl alcohol, however, is oxidized slowly by the body and may remain for several days. This characteristic makes wood alcohol generally undesirable for consumption. It is used in rubbing alcohol, antifreeze, and solvents and is considerably less expensive than ethyl alcohol.

Ethyl alcohol is highly soluble in water and fat but is relatively insoluble in protein. It passes through cell membranes readily and finds its way through the entire body in a short period of time. Pharmacologically, alcohol can have the effects of a sedative, a tranquilizer, a hypnotic, an anesthetic, or a narcotic, depending on the amount consumed.

Alcohol provides an instantly available source of energy. In calories per gram, it outranks carbohydrates and proteins. Unfortunately, it is intoxicating and devoid of vitamins and minerals. Thus, malnutrition is commonplace among alcoholics who would sooner drink than eat.

Volumes have been written on the harmful effects that are wrought by alcohol on the circulatory, respiratory, nervous, and digestive systems. These aspects of alcohol will be treated later in this work.

Nicotine

Intensive research involving nicotine has shown that it is in no way beneficial to the body. It has also been learned that nicotine alone cannot be blamed as the sole cause of the major killer diseases usually associated with smoking, namely, heart disease, cancer, and emphysema. The only conclusion that is reconcilable with the high rate of death among smokers is that it is caused by some substance in tobacco other than nicotine or possibly some substance in combination with nicotine. Since this work is to be limited to drugs and drug-like compounds, discussion here will be limited to nicotine, its effects and pharmacology.

It is interesting to note that most experts distinguish between the physical dependence of a smoker on nicotine and the addiction of the narcotics user. The smoker may become nervous and anxious without his cigarette and will eventually cause himself serious physical harm by smoking, but he is not addicted to smoking, experts say, because he can lead a normal life while continuing to smoke. On the other hand, the chronic user of narcotics, amphetamines, etc. will unquestionably behave and function in society in an abnormal manner. Herein rests the distinction between addiction and simple physical dependence.

A grain of nicotine taken orally is considered to be a fatal dose. Experimentally, it has been shown that the average smoker absorbs even more than this in a single day. If the nicotine absorbed by a typical smoker in a day were to be taken all at once, the effects would be fatal.

The amount of nicotine absorbed from the smoking of a single cigarette amounts to 1-2 mg. This quantity of nicotine is quite active physiologically.

Just exactly how much nicotine will be absorbed from a cigarette is directly dependent on whether or not the smoke is inhaled, how long the smoke remains in the mouth, and the depth of inhalation. Cigar and pipe smokers are likely to absorb almost as much nicotine as cigarette smokers because of the ease with which it slips into the cells of the mucous membranes of the mouth. Indeed, it is absorbed quite rapidly even by the skin. Studies of the nicotine in cigarettes show that some 22 percent of it reaches the mouth. The remainder either is burned off, escapes through the paper, or remains in the butt. When smoke is inhaled, about 90 percent of the nicotine that reaches the mouth is absorbed.

Considerable money has been spent by the cigarette industry to develop filters that would exclude nicotine and other harmful compounds from the smoke inhaled. It is generally agreed that these efforts are futile and serve more for advertising purposes than anything else. The industry's own researchers have said that an effective nicotine filter would not let any smoke come through either and, in addition, would be so expensive as to be impractical.

Solvents

It comes as a surprise to some that the inhaling of volatile chemicals is not new. Medical records reveal that as long ago as 1850 students were using nitrous oxide, chloroform, and ether to obtain "kicks." Interestingly, these three compounds were used illicitly for quite some time before

their value as anesthetics was discovered.

In recent years, the sniffing of glue for its intoxicating effects on the central nervous system has become popular. The active ingredients of glues and other mixtures are the solvents they contain. Most airplane glues, for example, contain the solvent toluene. Other mixtures that are used for the purpose of sniffing are fingernail polish and lighter fluid. The active parts here are xylene, benzene, and acetone. Lighter fluid contains naphtha, which is somewhat less toxic than the other solvents.

The usual approach to sniffing involves placing the chemical directly in a bag or placing a chemical-soaked rag in the bag. The opening of the bag is then pressed against the nose and mouth, and the contents are inhaled.

Asphyxia is a common result of this practice. Other effects may run from mild euphoria to coma and death.

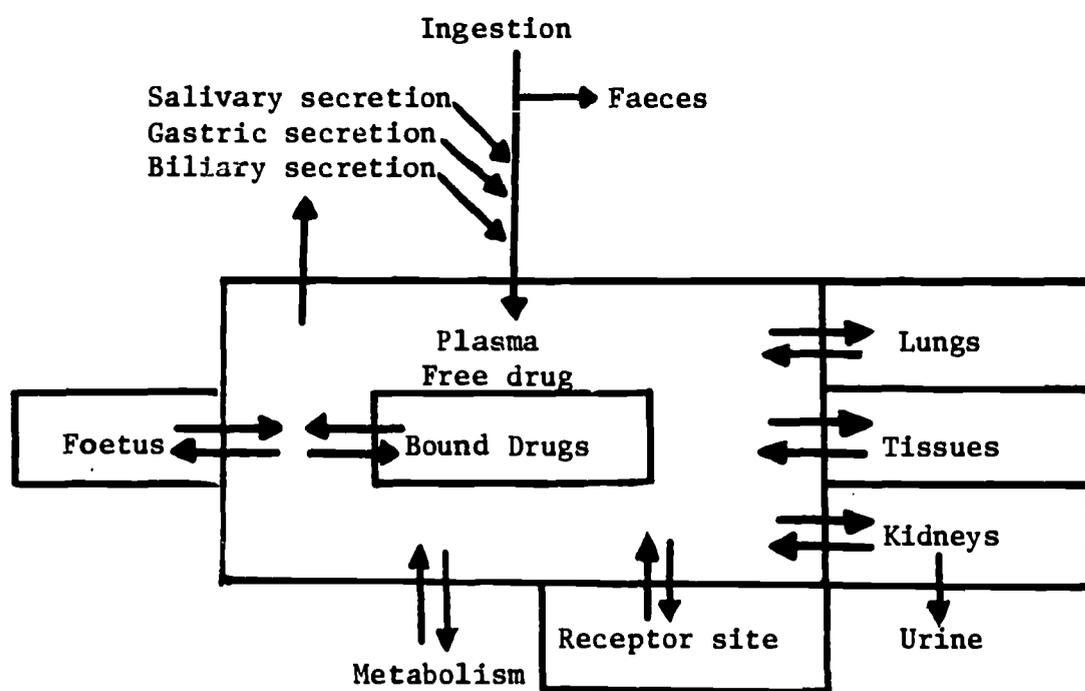
There is mounting evidence that the sniffing of glue can cause serious physical and mental damage. In addition to personality deterioration, bone marrow and liver damage are frequent effects of glue sniffing. Anemia is the most common manifestation of glue sniffing. It has been said the solvents can cause permanent damage to nerves by their effects on the fatty sheaths that cover them.

Gasoline sniffing creates dizziness, loss of coordination, and confusion. A side effect sometimes incurred is lead poisoning, which can lead to sterility and to mental and physical deterioration.

Amyl nitrite is prescribed for individuals with angina pectoris. It is illicitly used as a very short-term intoxicant.

Freon in itself is a harmless compound that is used as a refrigerant and

propellant for a wide variety of materials sold in aerosol cans. What apparently happens when it is used for kicks is that it displaces oxygen from the lungs. The result is a case of light-headedness, stupor, and finally coma. The user actually experiences a mild form of suffocation.



Drug pathways within the human body*

*Wolstenholme, Gordon and Porter, Ruth (eds.), Drug Responses in Man (Boston: Little, Brown and Company, 1967), p. 37.

The World Health Organization Expert Committee on Addiction-Producing
Drugs provided the following definition (1964).

Drug dependence is a state of psychic or physical dependence, or both, on a drug, arising in a person following administration of that drug on a periodic or continuous basis. The characteristics of such a state will vary with the agent involved, and these characteristics must always be made clear by designating the particular type of drug dependence in each specific case; for example, drug dependence in morphine type, or barbiturate type, or amphetamine type, etc.

SOME EFFECTS OF DRUGS ON CELLS

Drugs are ingested, absorbed in the gastrointestinal tract, and distributed by way of the blood to tissue fluids and finally to cells. Once inside cells, drugs are metabolized and either excreted in waste from tissues or distributed to other tissues.¹

The mechanisms involved with the passage of drugs are varied. Some make their way by means of simple passive diffusion.² Other drugs resemble endogenous substances in the cell and may be carried along by the transport systems of their analogues.³ Lipid soluble drugs pass into cells quite readily by diffusion.⁴

Some drugs are actively transported and may be built up in high concentrations in fetuses. An unfortunate example of this is the drug thalidomide. It reaches plasma concentration twenty times higher in the fetus than in the mother.⁵

It has been said that almost any molecule can get into the characteristically porous liver cell. It is also here that many drugs are metabolized, the products going either to the blood or directly into bile and then excreted.⁶

Cellular Effects of Depressants

Chlorpromazine has been shown to accumulate on cell surfaces and interfere with the passage of water through membranes. This has been demonstrated in vitro with the use of platelets, mitochondria, protozoa, muscle fibers, and nerve endings.⁷

Cells and the Effects of Alcohol

In spite of popularly accepted ideas concerning the effects of alcohol on cells, there is no conclusive evidence that structural changes occur in them as a result of using alcohol. Such cell damage is the result of long-term nutritional deficiencies that frequently accompany the chronic use of the drug and is identical to that which is found in nonalcoholics with⁸ vitamin deficiency diseases.

The osmotic relationship between cell and tissue fluid is affected by alcohol. The use of this drug in even moderate quantities causes a shift of water from cells to the fluids in which they are bathed.⁹

SKELETAL MUSCLE AND DRUG USE

Muscles and Drugs

Generally speaking, muscles are slow in taking up the drugs that are commonly abused. Other tissues of the body, such as those of the liver and the nervous system, seem to absorb disproportionately large concentrations of drugs before they overflow into muscle. This occurs in the case of alcohol. Only traces of this drug are detectable in muscle tissue even after alcohol has started its intoxicating action on the nervous system.¹⁰

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SOME CIRCULATORY ASPECTS OF DRUG USE

Under the influence of Cannabis, there is an increase in blood pressure caused by an increase in heart rate. The ciliary blood vessels of the eye dilate, causing the eyes to appear bloodshot.¹¹ This kind of response seems to be characteristic of the use of all hallucinogens.¹²

The initial effect of chlorpromazine is an acceleration of the heart rate (tachycardia) that is followed in a short period of time by a slowing of the heart rate. This final and most prolonged effect of chlorpromazine is a product of the depression of the heart rate control center of the brain. That the drug's effects come by way of the brain and not through direct influence by the drug on the heart is proven by vagotomy (cutting of the vagus nerve). When this is done, the presence of chlorpromazine in the body has no effect.¹³

Smoking one to two cigarettes causes the average individual's heart rate to increase fifteen to twenty beats per minute. There is a distinct rise in blood pressure and an increase in cardiac output. An interesting similarity can be noted between nicotine and epinephrine effects.¹⁴

The frequency of coronary heart disease is three times greater among smokers than among nonsmokers.¹⁵ Most authorities agree that smoking aggravates an already existing heart deficiency.

In effect, nicotine draws responses from the cardiovascular system that are similar to those elicited by the stimulation of the autonomic nervous system.

While an increase in cardiac output occurs under nicotine influence, there is a decrease in coronary blood flow. Thus there is an increase in

heart work while there is a decrease in blood supplied to the heart's own tissues. This, according to many heart specialists, aggravates an existing cardiac deficiency.¹⁶

Nicotine is believed to be the cause of Buerger's disease. This condition results from the constriction of blood vessels in the body's extremities. Severe cases may require amputation because of the gangrenous condition that may result. Buerger's disease is virtually unknown among nonsmokers.¹⁷

The ingestion of alcohol causes an initial increase in heart rate and blood pressure. This is followed by a depression of the total central nervous system and a drop in blood pressure and heart rate. Cerebral oxygen uptake is reduced.¹⁸

Blood vessels at the surface of the body are caused to dilate. In chronic users of alcohol, the blood vessels may become permanently dilated.¹⁹ This gives to the long-time alcoholic his characteristically reddened cheeks and cherry nose.

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SOME METABOLIC ASPECTS OF DRUG USE

The opiates are almost completely metabolized in the liver. The rate at which they are metabolized appears to be subject to a number of different factors. One worker has discovered that the rate of drug metabolism can be increased by injections of ACTH.²⁰

Generally, narcotics have an impairing effect on liver enzymes and slow down the activities of liver microsomes. Particularly affected are the oxidative reactions in liver cells.²¹ The use of morphine in persons with liver ailments presents a special medical problem and is discouraged by most authorities.²²

A common metabolic pathway is indicated for LSD and psilocybin and also for LSD and mescaline. This theory is based on the observation that when a user becomes tolerant to LSD he also becomes tolerant to psilocybin and mescaline.²³

After absorption in the gastrointestinal tract, LSD is rapidly distributed through the body with the highest concentrations occurring in the liver, brain, kidneys, and lungs. A very high concentration of LSD occurs in bile, which is probably an important means of excreting LSD. An inactive form of LSD is synthesized in the liver and excreted in bile.²⁴

Mescaline has an inhibiting action on the metabolism of carbohydrates, lactate, and pyruvate.²⁵ It appears that mescaline, norepinephrine, and serotonin all compete as substrates for the enzyme amine oxidase in the brain.

It has been theorized that aberrant metabolism involving normally occurring compounds as well as mescaline and LSD may account for the formation of chemical substances that cause mental disease. ²⁶

The active ingredient of marijuana is a compound known as tetra-²⁷hydracannabinol, also called cannabinol or simply THC. Experiments using C ¹⁴ labeled cannabinol reveal that most of the metabolic activity involved in Cannabis use occurs in the liver. It is found in lesser quantities in the brain despite the fact that it is here that it has its most pronounced psychedelic effect. ²⁸

One of the difficulties presented by THC is its instability. ²⁹ It breaks down to a totally ineffective form after a period of time. Because of this, there has never been a standard dose available for use by researchers. It is also ironic that, even though Cannabis has been in use for several thousand years and a problem for as long as it has been in use, very little research has been carried out on it. It is hoped that, in light of the recent surge in Cannabis use, there will be an increase in research on its specific effects on the body.

The effects of tranquilizers such as chlorpromazine are varied and numerous. One of these is its inhibiting effect on the enzyme alcohol dehydrogenase. This slows down alcohol metabolism and has the effect of increasing the alcohol content of the blood. Herein rests the danger ³⁰ of combining the uses of alcohol and depressants.

Evidence indicates that chlorpromazine has an inhibiting effect on the enzymes of the citric acid cycle. This, of course, means that it has a slowing effect on the body's total energy metabolism. ³¹

Mitochondria also are affected by chlorpromazine. More specifically, there seems to be a change of membrane organization during chlorpromazine use. These membrane structure changes also affect cytochrome oxidase activity. Oxidative phosphorylation and oxygen uptake by mitochondria are also interfered with.³²

It is known that body cells hydroxylate and deaminate amphetamines. The exact pathways followed in amphetamine metabolism, however, are vague.³³ The effects of the amphetamines on metabolism are similar to those elicited by epinephrine.

The liver is a limiting factor—a bottleneck, so to speak—in the metabolism of alcohol. It is here that the early stages in the oxidation of alcohol take place.³⁴

Alcohol is converted first to acetaldehyde, which is known to be a tissue poison. This compound persists for only a very short period of time, fortunately, for it is spontaneously converted to acetic acid. From this point, alcohol follows pathways that are typical of those that are followed by many other compounds. Ultimately, it is converted into carbon dioxide and water.³⁵

Alcohol is metabolized at a standard rate of about three ounces per hour. If alcohol intake does not exceed the rate of metabolism, there will be no ill effects from its use. Harmful effects are experienced, however, when intake exceeds the rate of metabolism. The level of intoxication from alcohol is in direct proportion to the degree at which intake exceeds metabolism. Since oxygen is required for the oxidative process, it follows that in high altitudes alcohol has a more intoxicating effect due to the rarified atmosphere.³⁶

Evidence of damage to the liver by alcohol is convincing. Cirrhosis of the liver is common among chronic heavy users and is not an infrequent cause of death among alcoholics.³⁷ Experiments using animals as subjects reveal a severe inflammation that occurs during heavy alcohol intake and a dangerous impairment of the liver's metabolic activities. There is no reason to doubt that those same changes occur in the human.

Physiological dependence occurs in heavy drinkers after a period of from three to fifteen years. Withdrawal from the use of alcohol by the alcoholic is not dissimilar to the syndrome demonstrated by the narcotics user.³⁸ Delirium tremens (the D.T.'s) that follows the withdrawal of alcohol after a period of heavy alcohol intake is believed to be caused by the lack of vitamin B¹² in the myelin sheath. This may also cause blackouts and hallucinations.³⁹

The products of nicotine metabolism appear in urine within a very short time after its absorption. This indicates that nicotine is metabolized very rapidly. Since no nicotine can be recovered from tissue after smoking has been stopped, it seems logical to conclude that no nicotine is stored.⁴⁰

Nicotine is an unstable molecule and undergoes changes that may include steps through a dozen or more different compounds before it finally appears in urine. One of the main intermediates in nicotine metabolism appears to be the compound cotinine which lacks the toxicity and potent pressor activity of nicotine. As a matter of fact, no evidence that any of the metabolites of nicotine are toxic has been presented to this date.⁴¹

An interesting theory has been offered to explain the withdrawal syndrome. It has been suggested that certain drugs induce the synthesis

of enzymes by elements of the central nervous system and at the same time they may inhibit the functioning of those enzymes. In other words, a drug may both stimulate the synthesis of and inhibit the function of that particular enzyme. Thus, when the drug is withdrawn, there is an excess of the enzymes. The presence of these excess enzymes may be manifested in the form of the withdrawal syndrome.

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A theory on drug tolerance involves the induction of the synthesis of enzymes that metabolize drug. For example, individuals who use the barbiturate phenobarbitone synthesize larger amounts of the enzymes that metabolize phenobarbitone. The more efficient the machinery for the metabolism of phenobarbitone, the more rapidly it is metabolized. The more rapidly it is metabolized, the lesser its effects. When a drug is metabolized before it can have its effects, the user has achieved full tolerance. The only way he can obtain the desired results is to take the drug in an amount that exceeds the ability of enzymes to break down the drug.

43

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SOME EXCRETORY ASPECTS OF DRUG USE

The presence of opiates in urine can be detected for as long as ten days after their use.⁴⁴ Urinalysis is one of the means by which law enforcement and medical authorities detect the users of opiates.

Opiates have a depressing effect on smooth muscle; thus, any activity calling for the use of this tissue will be negatively affected. Chronic users of narcotics, for example, frequently experience constipation as a result of the depressed condition of the smooth muscle of the gastrointestinal tract.⁴⁵

The excretion of narcotics is accomplished in a number of ways, among them through the kidneys, lungs, gastrointestinal tract, and bile. During metabolism enzymes oxidize, hydrolyze, and reduce drugs; but, while most drugs are metabolized and excreted in a changed form, some are filtered from the blood and excreted in urine in their original form.⁴⁶ The metabolites of drugs also occur in sweat, saliva, and the milk of nursing mothers.

The lungs excrete gaseous metabolites such as H₂O and CO₂. The biliary excretion of drugs has not been studied extensively. It is known that drugs in their original form and their metabolites can be removed from the bile of experimentally addicted animals.

The excretion of phosphates is reduced in users of LSD. This is an interesting point since the same difference in phosphate excretion has been observed in schizophrenics. Whether or not this is merely coincidental has not been determined.

The main pathway for the excretion of LSD and LSD metabolites is by way of bile. High concentrations of LSD occur in bile shortly after the administration of the drug. An inactive form of LSD also appears in bile.⁴⁸

Mescaline is largely excreted in urine. Unlike LSD, which appears only in minute quantities in urine, 60 to 90 percent of mescaline and its metabolites are excreted by way of urine. This is true also of psilocybin. Some psilocybin metabolites, however, are excreted by way of bile and feces. Most of the products of psilocybin metabolism are excreted within eight hours of its use, but a small amount of psilocybin is known to remain in the body for several days. Like LSD, psilocybin also reduces phosphate excretion.⁴⁹

Chlorpromazine increases urinary flow by increasing the excretion of sodium and water. It is likely that this results from a depression of the reabsorption process in the kidney tubule.⁵⁰

The excretion of hormones such as estrodiol, gonadotrophin, and estrone is inhibited by chlorpromazine. As a result, those hormones tend to remain in slightly higher-than-usual concentrations in the body.⁵¹

Alcohol has a diuretic action on the body by suppressing the secretion of those hormones that regulate kidney function. These hormones originate in the pituitary. The suppression of their secretion results in increased urine production. Alcohol also causes a shift in cell water to tissue fluid and increases blood lactic acid.⁵² With additional quantities of water in the blood, a greater amount of urine is produced. With the lowered PH created by increased lactic acid, the kidney increases its activities in order to carry out its function as a PH regulator. These effects of alcohol result in the loss of large amounts of water from the body. In heavy drinkers, this water loss is manifested in the insatiable thirst of the "morning after."

Since alcohol is almost completely metabolized in the body, the products of alcohol metabolism are hardly discernible in urine. A small amount of alcohol is excreted unchanged in perspiration and exhaled air.⁵³

Nicotine stimulates the flow of the antidiuretic hormone from the pituitary. The result is that kidney functioning slows down and less urine is produced.⁵⁴ In very high concentrations, nicotine causes several important compounds such as catecholamines to be filtered from the blood. Nicotine is known to stimulate peristalsis and may assist the movement of material through the intestines.

Caffeine acts as a diuretic and as such increases the flow of urine. It is found in minute quantities in coffee and in slightly larger quantities in some sleep-preventing mixtures.⁵⁵

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THE NERVOUS SYSTEM AND DRUGS

While the terrible effects of narcotics addiction on the nervous system are well known, it has never been shown that the use of opiates has any permanent effect on the central nervous system. When the user withdraws from drug use, the harm done immediately begins to disappear.

One of the effects of drug addiction is the adjustment of the nervous system to the use of a drug. The nervous system appears to increase its functioning in order to offset the effects of the presence of a drug. When the addict's nervous system reaches the point where it is able to function "normally" in the presence of a dose that previously caused a "high," he has developed a tolerance.⁵⁶ The user must then increase his dosage in order to achieve the desired effects. When the drug is withdrawn, the hyperactive brain and nervous system react violently. The result of this reaction, of course, is the withdrawal syndrome. When the nervous system is no longer dulled by the presence of narcotics, the user experiences cramps, nausea, sleeplessness, vomiting, and sweating. The point at which tolerance may be reached is dependent on the user, the drug, and the amount of the drug used.⁵⁷

Theoretically a level of tolerance could be reached that would be impossible to exceed. The only value of narcotics in this case would be to forestall withdrawal symptoms. Frequently addicts seek medical assistance at this point and will withdraw from drug use long enough to achieve a lower level of tolerance and cost.

Generally dependence requires that the drug be taken at regular intervals for a period of time that depends on the drug used. Morphine, for example, creates dependence in the user if used in small quantities for a week. Heroin, if ingested, must be taken at intervals of about twelve hours to produce dependence. Wide individual variations also exist.

Opiates depress the respiratory control center of the brain. Large doses given to nontolerant individuals may depress respiration and cause death. This occurs not infrequently among addicts, especially when the mixture being used is of unknown potency.⁵⁸

LSD seems somehow to increase the excitability of the central nervous system. Since it has long been known that neuron sensitivity is related to activities occurring in the synapses between nerve cells and that neurons are pharmacologically susceptible in these spaces, it is not surprising to find that the bulk of the research that has been directed toward LSD involves the physiology of the synapse.⁵⁹

Unfortunately the great amount of experimentation that has been carried out has yielded relatively little information, mainly, researchers say, because of the difficulty in designing experiments that will yield usable data. As best the information that has been gathered to date has been inconclusive and frustrating. Quite valuable data have come from experiments involving human subjects, but with the discovery of the permanently harmful effects of LSD this kind of work has been virtually abandoned.

A unique characteristic of LSD is its ability to mimic the neurohormone serotonin. It is known that serotonin is an important agent in the transmission of impulses across synapses. The interference of LSD with serotonin functioning could be the key to the activities of this psychotomimetic drug.⁶⁰

Another striking characteristic of LSD is its unusually potent effect on the brain. Less than one percent of a dose of LSD actually is absorbed by brain cells, yet it is 3,000 to 5,000 times more potent than an equal amount of mescaline.⁶¹

The visual effects of LSD are well known but little understood. It has been shown that LSD accumulates in rather high concentrations in the deeper visual cortex of an experimental animal and influences the transmission of visual impulses to the thalamus.⁶² The sensitivity of the retina to light stimuli is also increased. The auditory effects of LSD are quite pronounced as evidenced by the quantities of the drug that are found, for example, in the cochlea.⁶³

There are indications that LSD "triggers" a reaction that continues long after it is completely metabolized and that certain effects persist in such a way as to permit a reoccurrence of the symptoms of LSD use.⁶⁴

Several conclusions concerning the functioning of LSD are evident. It probably disrupts those areas of the brain that discriminate between useful and useless information. It prevents the user from focusing attention on one activity or one event and allows an interplay of the information that comes to the brain. The integrating activity that normally takes place in the brainstem stops because of the inability of synapses to function normally. Considering these events one can envision how LSD might create the profound mental disturbance for which it is known.

Tolerance to LSD develops rapidly. In one week of regular use, a previously adequate quantity of the drug no longer produces the desired effect, and the dose must be increased. When a user becomes tolerant to LSD, he also becomes tolerant to mescaline and psilocybin. This is known as cross tolerance.⁶⁵

The evidence indicates that the mechanisms of LSD, psilocybin, and mescaline are the same. A difference exists in the degree to which a given amount affects the user.

The symptomatic effects of THC from Cannabis are well known. The physiochemical effects, however, are still under study and as yet are not well understood. It may be that Cannabis produces its effects in the same way that is employed by other psychotomimetics. The eventual effect, then, of Cannabis involves the neurohormones that function in interneuron communication. It is believed that THC directly affects the functioning of the enzymes that work with the neurohormones and in this way change the functioning of the hormones.

Chlorpromazine inhibits the function of acetylcholine, an important neurohormone, and interferes with ATP-ASE in oxidative phosphorylation in brain nerve cells.⁶⁶

The functioning of the hypothalamus is impaired, with the result that hypothalamus-controlled activities such as that involving temperature regulation are disrupted. Under these conditions, the temperature fluctuates abnormally.⁶⁷

As a result of the depression of brain stem activities, individuals who have taken depressants are less responsive to environmental stimuli. Maze-running speed in experimental rats is greatly reduced, and in humans the vomiting center in the medulla is depressed.⁶⁸ One problem created here is very obvious. If a person has taken an overdose of a depressant (chlorpromazine in particular) it becomes difficult to induce vomiting.

A potent tranquilizer called reserpine has been found to be a very effective sedative for use in the treatment of the mentally disturbed. It appears to act by depleting the supply of serotonin and catecholamine, two chemicals that function in synaptic transmission.⁶⁹

Barbiturates are depressors of the central nervous system, but how they accomplish their depressing action is largely unknown. There is some

evidence that these barbitol-related compounds stabilize membranes and inhibit the changes in membrane polarity that are the nerve impulses. This dulls nerve cells so that they are not as readily excited by environmental stimuli. Their action is further enhanced by slowing the recovery time following the transmission of an impulse. Thus the shower of nerve impulses that might ordinarily delay sleep and keep the user continually aware of this environment are partially shut out.⁷⁰

Barbiturates have a strong depressing effect on the respiratory control center of the brain. For this reason the combination of barbiturates and alcohol (another central nervous system depressant) is occasionally fatal as a result of the complete depression of respiration.

Current data seem to indicate that the amphetamines bring about their effects by causing the release of neurohormones stored in nerve endings. This causes the user of amphetamines to be highly excitable and receptive to stimuli. The postdepressive phase of amphetamine use is a result of the depletion of neurohormones with no "reserve" being available for use by the nervous system. The overall effect is the slowing down of the total central nervous system.⁷¹

In recent years neurophysiologists have become intrigued with the theory that the chemical manipulations of the neurohormones of the brain may be a means of treating mental illness. This is based on the hypothesis that many forms of dementia have their origins in abnormal brain chemistry. If this is correct, then the patient could be cured by administering chemicals to remedy his abnormal chemistry. For example, the right kind of stimulant could cure the depressed patient, the right kind of depressant could cure the hyperactive patient. This is an oversimplification of this possible

approach to the treatment of mental disease, but many specialists working in this area are pursuing its potential.

The effect of alcohol is to suppress the entire nervous system. The level of effect is proportional to the amount of alcohol consumed, with the range of depression going from mild disorganization of thought processes and loss of coordination to loss of consciousness, coma, and even death.⁷²

Even when taken in amounts sufficient to kill, the effects of alcohol seem to concentrate on the reticular activating system. Thus, the cerebral cortex becomes less organized, and activities requiring alertness and coordination cannot be performed effectively.⁷³

The brain has a high affinity for alcohol. Within half a minute of its ingestion, alcohol can be detected in the brain's cells. Precisely how this drug goes about causing intoxication is not known. A widely (but not universally) accepted theory describes its action as interfering with synaptic transmission. This explains the effects of the drug, but exactly how this blockage occurs has yet to be adequately explained.⁷⁴

Nicotine has a pronouncedly stimulating effect on ganglion nerve cells. This is followed by a state of depression that continues until the nicotine is completely metabolized. The initial reaction of brain nerve cells is one of excitation. This is followed by depression of brain nerve cells.⁷⁵

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SOME EFFECTS OF DRUGS ON HOMEOSTATIC MECHANISMS

The use of LSD causes a serious increase in temperature (hyperthermia). Most of the deaths resulting from LSD use have been caused by this temperature increase. There is also a disruption of the normal metabolism of glucose that is reflected by a drop in the blood-glucose level (hypoglycemia).⁷⁶

It has not yet been determined pharmacologically whether Cannabis is a stimulant or a depressant. It has been shown, however, that its use is followed by a state of hypothermia and hypoglycemia.⁷⁷

The use of chlorpromazine depresses the temperature control of the brain (the hypothalamus). This produces a condition of hyperthermia or hypothermia, depending on the environmental temperature. This is a direct result of the disruption of heat loss and heat retention.⁷⁸

Alcohol causes the blood vessels on the surface of the body to dilate. Thus, large amounts of heat are permitted to escape and the body tends toward hypothermia. This obviously is contrary to the commonly held illusion that alcohol causes an increase in body temperature.⁷⁹

The fluid balance between cells and tissue fluid is also disrupted. Water is drawn from cells into the tissue fluids. This results in a slight dehydration of cells. The chronic use of alcohol is believed to promote the formation of fatty tissue in the liver.⁸⁰

Intoxication is accompanied by the production of larger than usual amounts of lactic acid. This causes a drop in the PH of the blood and contributes further to the dehydration process by causing the kidneys to produce more urine in carrying out its PH regulating function.⁸¹

The nicotine in one to two cigarettes causes constriction of blood vessels in fingers and toes and a reduced flow of blood to these areas. This amount of nicotine also causes a slight elevation of blood sugar.⁸² Temperatures in the fingers and toes of heavy smokers have dropped as much as 6°F. degrees during smoking.⁸³

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THE ENDOCRINE SYSTEM AND DRUGS

The effects of tranquilizer use on the endocrine system are numerous. Only a few of these will be discussed. The mechanism operating here usually involves a disruption of the homeostatic devices involved with the regulation of the blood-hormone level.

Prolonged use of chlorpromazine is known to inhibit the secretion of ACTH.⁸⁴ It also is known to depress the hypothalamus, with the result that the secretion of the lactogenic hormone from the anterior pituitary goes uncontrolled. Individuals who are chronic users of this drug may experience lactation even though no pregnancy exists.⁸⁵

Other effects include abnormalities in the secretion of the luteinizing hormone, the follicle-stimulating hormone, ACTH, the thyroid-stimulating hormone, and thyroxine. Obviously, some of the above effects are likely to result in the disruption of the menstrual cycle and occasionally produce symptoms similar to those experienced during pregnancy.⁸⁶ Also, during pregnancy, chlorpromazine suppresses the secretion of chorionic gonadotrophin and pituitary gonadotrophin.⁸⁷

In experiments involving the use of rats, it was discovered that there are sex differences in drug metabolism rates. Male rats were able to metabolize barbiturates more rapidly than female rats. Since castration reduced drug metabolism in these animals, it was concluded that the male hormones are somehow involved.⁸⁸

In humans it has been learned that testosterone extends the effective time of barbiturates and that the use of oral contraceptives containing progesterone impaired the metabolism of chlorpromazine by human females.⁸⁹

The high concentrations of nicotine in the blood that follow heavy smoking stimulate the flow of epinephrine from the adrenal glands. This has the effects usually associated with normal epinephrine secretion. Several workers noted that there is an interesting parallel between the overall effects of nicotine and those of epinephrine. It requires, however, one thousand times the dose of nicotine to produce the same effects as a given amount of epinephrine.⁹⁰

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SOME GASTROINTESTINAL ASPECTS OF DRUG USE

Opiates diminish the appetite, with the result that addicts often are emaciated and suffer from malnutrition, a condition that is frequently associated with alcoholism.⁹¹

LSD is absorbed rapidly in the stomach and small intestine. Within an extremely short period of time, a high concentration of it begins to build up in the liver. Concentrations of LSD in the organs peak within ten to fifteen minutes after ingestion.

In cases of extremely heavy smoking or where the smoker is new to the habit and has not built up a tolerance to nicotine, one of the effects of nicotine is often nausea and emesis.

Nicotine, along with the other components of cigarette smoke, is swallowed with saliva from the mouth. There is some evidence in experimental data that this predisposes the stomach to cancer. The irritation of stomach mucous membranes and the artificial stimulation of gastric juice secretion by nicotine is believed to result in irritation to the stomach lining and eventually ulcers.⁹²

It is generally agreed that nicotine stimulates peristalsis and augments intestinal activity. In so doing, it may assist in digestion. It cannot be said, however, that smoking is beneficial to the digestive process, because there appears to be no real consistency to date on this problem. Smoking more often is associated with diarrhea, constipation, and emesis.

Nicotine has an appetite-suppressing effect that is similar to that of amphetamine. Individuals who stop smoking report a return of appetite, greater appreciation of the food they eat, and a gain in weight.

The caffeine in coffee stimulates the secretion of gastric juice, and its use by persons with ulcers is not recommended. Generally, coffee and tea (both of which contain caffeine) stimulate peristalsis in such a way as to assist in the digestive process.⁹³

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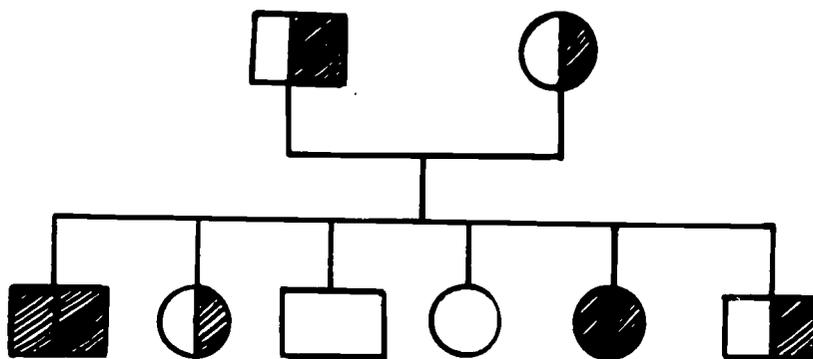
GENETIC ASPECTS OF DRUG ABUSE

The effect of drugs varies between species. In the cat an injection of morphine causes excitation; in the dog it has a sedative effect.

A similar range of effects occurs within the human species. Some react to a particular narcotic, for example, with excitement. Another may promptly fall asleep. It has been suggested that these differences in drug response are genetic in nature.⁹⁴

While no research has been done that yields conclusive evidence that drug response is an inherited factor, it has been shown and well substantiated by experimental data that differences in the ability to metabolize sugar, proteins, etc. are inherited. These differences have been related to the presence of aberrant enzymes which, of course, are inheritable and which may manifest their presence in some obvious form such as an allergy or even death.

Abnormalities in the enzymes that metabolize drugs would necessarily produce abnormal response to drugs. It has been said that, if the genetics of all of drug response could be worked out, the information gained could be projected into the study of population genetics, and predictions concerning the frequency of certain drug responses within a population could be made.



The chart is the pedigree of a family having abnormal cholinesterase, an enzyme involved in the metabolism of succinylcholine, a drug used in anesthesia. Those members of the family who are homozygous for the characteristic will show prolonged response to the injection of succinylcholine.⁹⁶ Three different forms of defective cholinesterase are known.

Several other examples of monofactorial inheritance of drug response have been studied. One of these results from a deficiency of glucose-6-dehydrogenase in erythrocytes. In this case the use of the drug primaquine is followed by hemolysis.⁹⁷

The first evidence of the possible effects of LSD on genetic material came as a result of in vitro studies of human leukocytes. The aberrations thus discovered generally were in the form of broken chromosomes. Later chromosomal abnormalities were discovered in the circulation leukocytes of several "hippies" on the West Coast. It has not as yet been determined whether or not these defects are permanent or short-term changes. Considerable alarm is warranted because of the similarity between the chromosomal abnormalities resulting from LSD use and those seen in survivors of the Hiroshima bomb blast and in persons who have been exposed to ionizing radiation. Both types are likely to develop a leukemia-like syndrome. The same changes in chromosomes have been observed in users of psilocybin.⁹⁸

There is an indication that LSD use can cause birth defects. One worker reports chromosome breaks in 50 percent of infants who were exposed to LSD in utero. A rare defect in which the brain herniates through the incompletely fused skull has occurred several times in fetuses that were exposed to LSD early in pregnancy.⁹⁹

SOME REPRODUCTIVE ASPECTS OF DRUG USE

The use of opiates reduces sexual activity and produces orgasmic impotence in men. In women, opiates can cause infertility and amenorrhea (suppression of menstruation).¹⁰⁰

During pregnancy, the opiates are transported into and out of the fetus along with other materials. The speed with which this occurs depends on such factors as rate of diffusion, speed of blood flow, and the drug level in maternal blood. Given sufficient time, the drug plasma ratio of the fetus will be the same as that of the mother.¹⁰¹

This leads to an unfortunate aspect of drug abuse, that of congenital neonatal narcotics addiction. Infants born to addicted mothers are immediately faced with the risk of death from the physiological strain of the withdrawal symptoms, the direct depressant action of the opiates, or abnormalities resulting from faulty development in an addicted mother. No standard treatment exists for this danger. Generally, however, narcotics are used to control withdrawal symptoms.¹⁰²

Infants born of addicted mothers are generally smaller by weight and premature. The relationship between prematurity and maternal addiction is not understood.¹⁰³

There is no evidence that alcohol has any effect on the reproductive organs.¹⁰⁴ It is a statistical fact, however, that the birth rate among alcoholics is higher than that of temperate or abstinent parents. Alcoholics also tend to have miscarriages more often, and the death rate of children under five years of age is higher among alcoholic families. Scientists believe that these effects reflect a high degree of indifference to family responsibilities on the part of alcoholic parents.¹⁰⁵

During pregnancy, nicotine is transferred to the developing fetus and appears to have the same effect on the fetus as on the mother.¹⁰⁶

According to statistics, women who smoke bear smaller babies than non-smoking mothers. It is believed that this is the result of constriction of placental blood vessels which reduces the flow of blood to and from the fetus.¹⁰⁷

The nicotine from smoking appears in the milk of nursing mothers within minutes after smoking is started. The amount of nicotine present is in direct proportion to the number of cigarettes smoked.¹⁰⁸

Studies have shown that the fetal death rate for nonsmokers in Germany was 6.4 per thousand births. Among smokers, the fetal death rate is approximately 15.5 per thousand. Another study shows that the rate of premature birth is greater among smokers than among nonsmokers.¹⁰⁹

Strains of mice that metabolize barbiturates more rapidly than ordinary mice have been developed. It has also been shown experimentally that some strains of animals are extremely slow metabolizers of barbiturates. This indicates that the ability to metabolize barbiturates is under genetic control. There is believed to be a range in the kinds of enzyme systems that goes from the efficient to the inefficient. Defective enzymes are almost certain to be involved where the ability to metabolize certain drugs is weak or entirely absent.

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