DRUGS AND THE MIND

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Introduction

For purposes of this discussion, the mind, or psychoses, is the thought processes involved in meeting the problems of life. These processes are fundamentally biochemical, and a good review of current knowledge about these biochemical processes has recently appeared (6). In this paper, I plan to review briefly the history of the discovery of psychopharmacological agents, wtih some discussion of drugs commonly used, which have some affects on the mind. A technical solution to a major societal problem may lead to new problems, and the history of this event can be used to illustrate how some useful drugs were discovered, and provides an opportunity to discuss the relationship of biological activity to molecular structure in certain compounds.

Recognition of the Problem

By 1950, it was recognized that admissions to mental hospitals in the United States was increasing at a rate of ten to twelve thousand per year and that if this rate continued, it was projected that every hospital bed in the United States would be occupied by a mental patient by the year 1970. These figures were useful in getting increased Federal funding for hospital construction. In 1950, treatment for mental disease was basically custodial care, which could be very expensive, as these patients were frequently destructive. Historically there were two different treatments developed for this disease, commonly felt to have supernatural overtones, and be the result of possession by evil spirits. The skulls of primitive men somethimes show that they had holes drilled in the forehead, to let out the evil spirits. In 1950, a patient might be treated by a surgical procedure, Frontal Lobotomy, in which a hole was drilled in the forehead, and the frontal part of the brain destroyed. Another treatment, used in the Middle Ages, involved lowering a mentally disturbed person into a pit of vipers, tied by the ankles, so that the head came near the dangerous animals. When properly done, the patient would go into shock, and on recovery seemed much improved. In 1950, electroshock or insulin shock therapy was frequently used, with similar results.

In 1955, the U.S. Public Health Service reported that 559,000 beds were occupied by mental patients, and they anticipated an increase of 12,000 by 1956. However, in 1956 the number of beds occupied by mental patients was down by 7000, and there has been a steady decrease since then despite a population increase. The use of electoshock therapy has been cut by 80-90% (2).

Psychopharmacological Agents

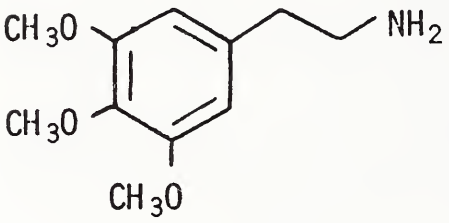
The reason for this sudden reversal of the trend in hospital bed occupancy by mental patients has been called the most significant development in chemotherapy since Penicillin. It was the discovery that mental disorders could be treated by chemcial substances, and that mental disease may be a metabolic disturbance, comparable to other metabolic disorders, such as diabetes. This represents a breakthrough in thinking about mental disease, as the general populace still, in the middle 1950s attributed some supernatural character to mentally disturbed patients. "He behaved like a man possessed", they would say. It is interesting that this breakthrough in thinking about

*Indiana Academy of Science "Speaker of the Year," 1983-84

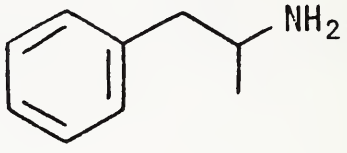
mental disease, i.e. that it might be treatable with chemicals, had not occurred earlier. Afterall, chemical agents affecting the psychoses had long been known and used for that purpose.

Hallucinogens

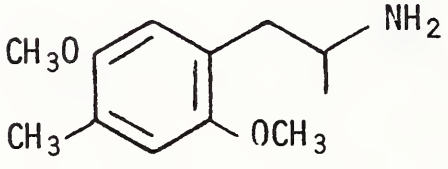
The early Greeks described the Eleusinian Mysteries, describing strange dreams by those who partook of potions in the city of Eleusis, The Hashishin, or assassins, were eaters of hashish, extracted from Cannabis Indica. The Norse Berserkers achieved the proper mental state for reckless attack by eating certain mushrooms, and certain



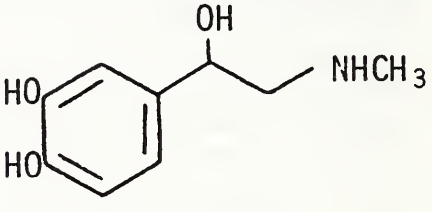
mescaline



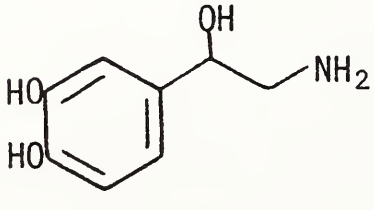
benzedrine
(amphetamine)



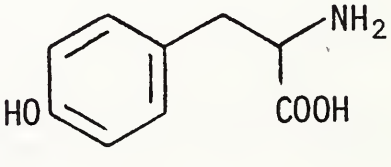
STP



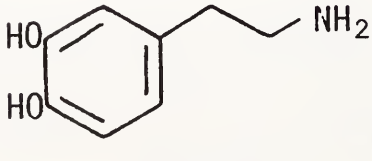
adrenaline
(epinephrine)



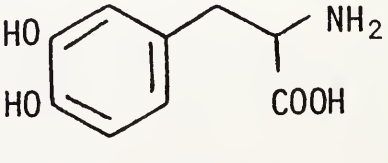
norepinephrine



tyrosine



dopamine



L-Dopa

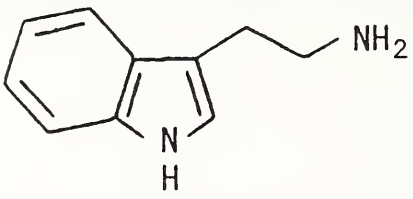
FIGURE 1.

voodoo cults used oloiuqui, an extract of Morning Glory, for religious hallucinations. These are all psychadelic drugs, and contain chemical agents which cause hallucinations and irrational behavior. In our own southwest, the Mescalero Indians have long used the mescal cactus to induce a religious mood in Native American church ceremonies. The mescal cactus contains mescaline (see Figure 1), the structure of which was established in 1900. The nature of the hallucinations caused by mescaline, "dreams in Technicolor", is beautifully described by Aldous Huxley in "The Doors of Perception" (5). Benzedrine, having an *alpha*-methyl group (see Figure 1) is about ten times as potent as mescaline as a psychomimetic agent, but the hallucinations are not the same. A synthetic substance called STP on the street (2,5-dimethoxy-4-methylphenylisopropylamine, see Figure 1) is about one hundred times as potent as mescaline in causing hallucinations, so that five to ten milligrams gives the effect. The drug benzedrine, or amphetamine, is commonly used as an appetite suppresant (anorexant) and central nervous system (CNS) stimulant. At low dosage (10 to 20 mg.) it serves to keep one awake. The danger is overdosage. Fifty to one-hundred milligrams can have serious psychomimetic effects, so it is about ten times mescaline in activity as a hallucinogen.

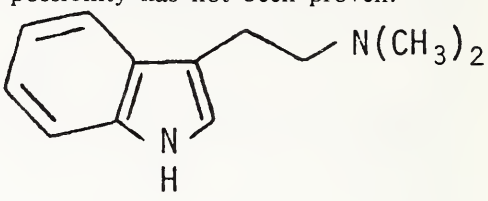
It is interesting to compare the molecular structure of these hallucinogens to substances which occur normally in the body. Adrenaline (epinephrine, Figure 1) is the hormone which causes increased wakefulness and increase in blood pressure, heart rate and respiration, and is released from the adrenal gland in response to fear or excitement. Norepinephrine (Figure 1) is an important neurotransmitter, or "brain hormone". Both of thse compounds are derived from the essential amino-acid tyrosine, by enzymatic hydroxylation and decarboxylation to form the highly active norepinephrine, which is then stablized by methylation to form the less active epinephrine. Another important neurotransmitter is dopamine (Figure 1). This substance is also derived from tyrosine *via* the dihydroxamino-acid, L-Dopa, and a deficiency of this nerotransmitter causes Parkinson's disease. These compounds are all members of the family of β -phenylethylamines, which in general have central nervous activity. Note how "mere molecular modification" changes the properties of these molecules. Methylation at the *alpha*carbon increases activity by slowing down metabolic degradation of the amine group. Methylation at the nitrogen decreases activity.

A second group of CNS active agents are members of the *Beta*aminoethylindole class (Figure 2). The simplest of these is tryptamine, a mild CNS stimulant which can occur naturally. Conversion of this to dimethyltryptamine (Figure 2) produces a powerful psychotomimetic. This compound is closely related to two other naturally occurrring hallucinogens, bufotenin, found in toad skins and certain plants along the Orinoco river, and psilocin, whose phosphate ester is psilocybin, the active principal of the Mexican sacred mushroom ("God's flesh") *Strophariaceae agaricales* (1). These compounds are structurally related to the normal brain hormone, serotonin (Figure 2). Serotonin, or 5-hydroxytryptamine, was originally identified as "enteramine" in the 1930s, a stimulatory substance present in the intestine which caused constriction of intestinal tissue. Its structure was determined in 1949, and its presence in brain in low concentration reported in 1952. At that time it became the subject of intense investigation, so that in 1965 alone, over one thousand papers on serotonin appeared in the scientific literature (3). It turns out that serotonin is widely distributed, occurring in many plant and animal tissues, such as banana skins. It is produced in the brain by decarboxylation of 5-hydroxytryptophan, an amino-acid formed by hydroxylation of the essential amino-acid tryptophan (Figure 2). However, perenteral administration of serotonin does not have any effect on the brain, as it does not pass through the blood-brain barrier. An excess or deficiency of serotonin is held responsible for many mental conditions. It is reasonable to assume that abnormal metabolism of serotonin,

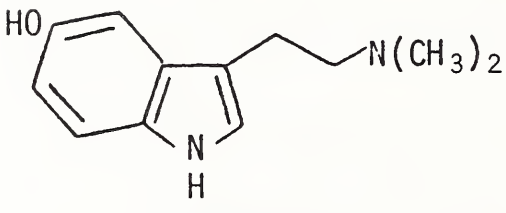
involving N-methylation, might produce the powerful hallucinogen bufotenin, thus causing some mental disturbance. However, this possibility has not been proven.



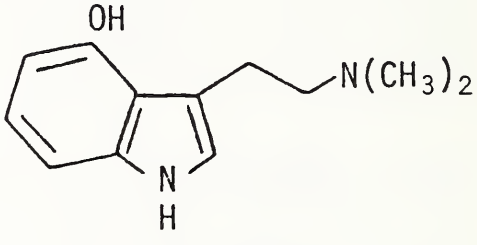
tryptamine



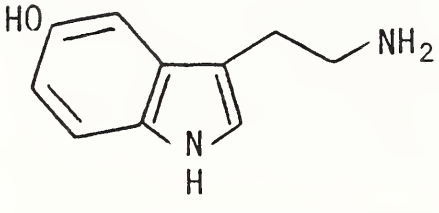
dimethyltryptamine



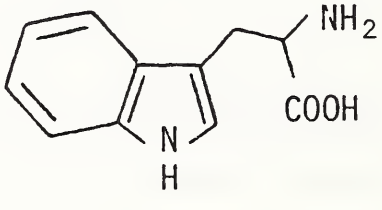
bufotenin



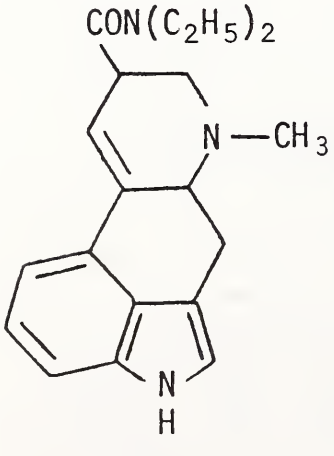
psilocin



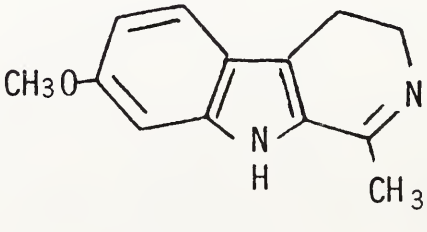
serotonin



tryptophan



LSD



harmaline

FIGURE 2.

The most potent hallucinogen known is d-lysergic acid diethylamide (LSD, Figure 2). It was discovered by Hoffman, who accidentally inhaled the dust of some of this recrystallized synthetic lysergic acid derivative. Later research established the fact that LSD was about 20,00 times as potent as a psychotomimetic agent as mescaline, being active at microgram levels (4). It is interesting that the active principal of *Rivea corymbosa*, or ololiuqui, a hallucinogenic plant used by Central American Indians, and known since the sixteenth century, also contains lysergic acid amides, although this fact was not established until 1960 (4). The amides present in ololiuqui are not so potent as LSD, however. Another alkaloid, from the leaves of *Malpighiaceae*, was used by South American Indians to prepare a hallucinogenic drink, called "ayahuasca" or "caapi" (1). It contains harmaline (Figure 2) a compound which found some use by physicians early in this century as an antidepressant. It is a powerful monoamine oxidase (MAO) inhibitor, and excess causes hallucinations, so it is no longer used clinically. It should be noted that both the lysergic acid derivatives and the harmala alkaloids are *beta*-aminoethylindole derivatives, although they differ by being held in different rigid structures.

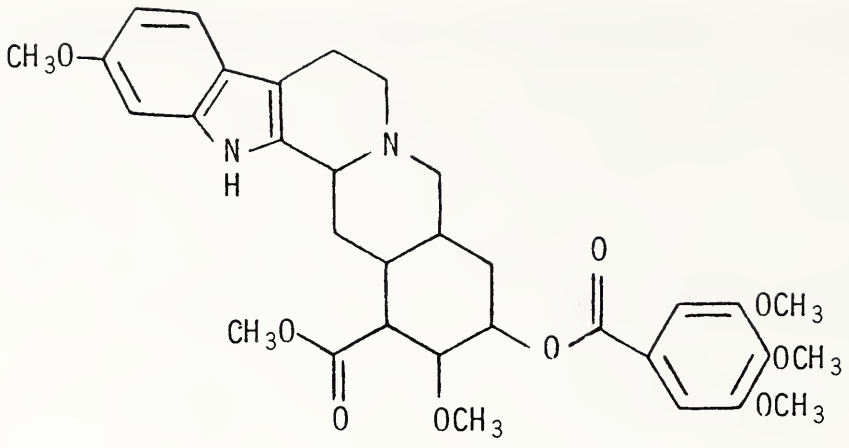
Tranquilizing Agents

We should now consider what happened to cause the sudden drop in hospital bed occupancy by mental patients which occurred in 1956. Although serotonin was under active investigation, and substances causing mental disturbance were well-known in folk medicine, terms such as "psychopharmacology", and "hallucinogen" had not been coined. The first tranquilizers or ataractic agents, reserpine and chlorpromazine, were discovered by accident, and it was these two which accounted for the spectacular decrease in hospitallization of mental patients.

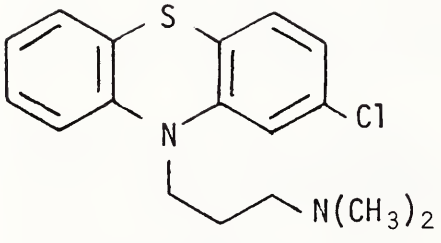
Extracts of the plant *Rauwolfia serpentina*, or Snake root, had long been used in India by holy men, to induce a trance-like condition during meditation. Colicky babies could be calmed with it, and it was used by Hindu physicians to lower blood pressure in patients with hypertension. Its use in the treatment of insanity by the Hindus is mentioned in western literature as early as 1755 (1). In 1947, Emil Schlittler and co-workers in Ciba, in Switzerland, began to investigate the alkaloids of *R. serpentina*, and by 1952 they had isolated and crystallized reserpine (Figure 3). Soon afterward pharmacologists reported that reserpine had both tranquilizing and antihypertensive properties. In testing on human patients, it was observed that the drug not only lowered blood pressure, but relaxed the tensions and anxieties which often accompany hypertension. In 1954, it was reported that reserpine was useful in treating psychotic patients, particularly those who are severely agitated and hyperactive. Note that reserpine (Figure 3) also belongs to the family of *beta*-aminoethylindoles, like those in Figure 2, but has a second complex portion of the molecule.

Chance, plus some astute clinical observations of the action of a drug useful for another purpose, played a major role in the discovery of the tranquilizer chlorpromazine [2-chloro-10(3-dimethylaminopropyl)phenothiazine, Figure 3]. Related phenothiazine derivatives had potent antihistaminic activity, and in searching for structural modifications of this drug, chlorpromazine was synthesized and found to have utility in motion sickness, but was very sedating. It was marketed in the United States for the treatment of nausea and vomiting in 1954, but it was soon discovered that its greatest utility was in the treatment of psychotic states. It is known that both reserpine and chlorpromazine can block the effects of LSD.

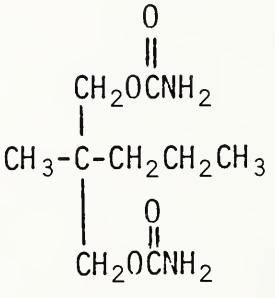
Still a third compound which had useful CNS effects was introduced in 1955, under the name Miltown (meprobamate, Figure 3). This was a mild "antianxiety" agent, or minor tranquilizer, which also has muscle relaxant properties. It was originally



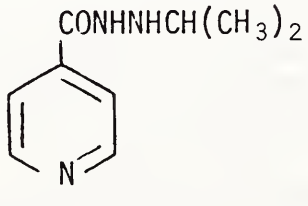
reserpine



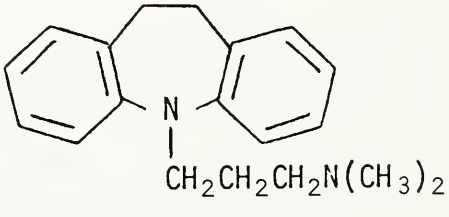
chlorpromazine



meprobamate



iproniazid



imipramine

FIGURE 3.

dispensed as an "over-the-counter" drug, and was widely used. It was the wide use of tranquilizers which prompted Dr. Nathan S. Kine, of Rockland State Hospital, to say,

> "A snarling vicious animal can be transformed by a few milligrams of a chemical into a friendly tranquil happy pet - a pleasure to have in captivity, but wouldn't last ten minutes in the jungle! Mankind may tranquilize itself into oblivion" (2).

It was the effect of known tranquilizers on animals that allowed the development

of second and third generation mild tranquilizers, such as the benzodiazepines (Valium, Librium, etc.). The pharmacologists now divide the ataractic agents (tranquilizers) into two groups, the major tranquilizers, (antipsychotic or neuroleptic agents) such as reserpine or chlorpromazine, and the minor tranquilizers, or antianxiety agents, such as meprobamate or benzodiazepam.

Antidepressants

Clinical reports on antidepressants, or analeptic agents, the so called psychic energizers, appeared in 1957, only a few years after the discovery of the antipsychotic drugs. There are two major classes, the MAO inhibitors, and the phenothiazine alalogs. Both were discovered accidentally, during searches for other drug types. During clinical studies of iproniazid (Figure 3) as an antituberculosis agent a mood-elevating effect of this drug was seen. It was soon found that iproniazid was a potent MAO inhibitor, thus preventing the destruction of norepinephrine and serotonin in the brain, and preventing the fall of these biogenic amine levels induced by reserpine. It was therefore used in the treatment of depression. However, iproniazid and related MAO inhibitors can cause severe rises in blood pressure, and they are not widely used today.

The tricyclic compounds structurally related to the phenothiazine class of antipsychotic agents (e.g. chlorpromazine, Figure 3), of which imipramine (Figure 3) is the primary example, were also discovered accidentally, while searching for antihistamines, sedatives and analgetics. The discovery of chlorpromazine prompted the testing of imipramine as an antipsychotic drug. It was relatively inactive in this regard, but instead appeared to have specific therapeutic value in the treatment of depression. Imipramine and related compounds are now the drugs of choice in treating depression. The earlier treatments involved the use of the hallucinogens harmaline and amphetamine, as previously noted.

Availability of New Drugs

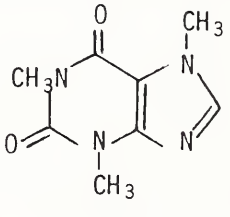
The history of the discovery of the psychopharmacological agents illustrates the fact that for new breakthroughs in drug therapy to occur, it is important that new drugs be available for human administration. Without reserpine for high blood presssure, or chlorpromazine as an antihistaminic, their action on mentally disturbed humans would not have been detected. Animal tests were only useful after the establishment of the pharmacological activity. In 1962, the Food and Drug Administration adopted new regulations requiring proof of efficacy as well as safety, before a new chemical entity could be introduced into clinical use. This reduced the number of new chemical entities introduced as drugs by more than half, 641 in the fifteen year period 1947-1962, versus 247 in the fifteen year period 1962-1976, as reported by the Pharmaceutical Manufacturers Association. Because a drug is not equal or more potent than a currently used drug does not mean that it will not be useful, and it may well have other more valuable properties.

Commonly Used Central Nervous Agents

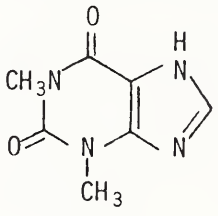
The availability of these central nervous agents led one pharmacologist to predict, "Soon people will titrate themselves awake with an analeptic agent, and at the end of the day, relax with an ataractic agent." However, people have long practiced that very thing. A couple of cups of coffee gives one enough central nervous stimulant, caffeine (Figure 4), to start the day wakeful, with perhaps booster doses in the middle of the morning and at noon. In the late afternoon, one or two cocktails produces a blood level of about 0.05% blood volume of alcohol, which induces a relaxed state mentally and a warm feeling due to mild peripheral dilation. Indeed caffeine is the most widely used drug in the world. In the U.S. we consume about seven million

kilograms per year. Many soft drinks, both brown and white, contain from 25 to 55 mg. of caffeine per ten ounce container. The toxic does, or LD_{50}, of caffeine is 150 mg/kg in rats. This is about the amount present in one cup of rich brewed coffee, so an average one hundred fifty pound human might die after consuming seventyfive cups of strong coffee at one sitting. Indeed, it was illegal to drink coffee, a dangerous drug, in Arabia in the fifteenth century.

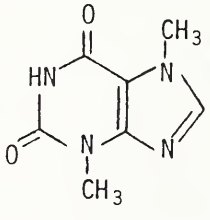
It is instructive to compare the activity of the three xanthines commonly present in both coffee and tea. The other two are theophylline and theobromine. All three have diuretic properties, and effect the brain, heart, and skeletal muscle. However, the minor molecular modifications shown by the varying positions of methyl groups (Figure 4) causes interesting differences in their activity. Caffeine, which is present as the major constituent of the xanthine mixture in coffee, exhibits predominantly central nervous activity. Theophylline was used clinically as a diuretic, since its effect on the kidneys and heart rate is more pronounced, while theobromine has a greater effect on skeletal muscle and as a vasodilator. Since, while tea does contain caffeine, the other two xanthines are the major constituent of the alkaloids in tea, drinking tea is more apt to be relaxing, causing a warm feeling. Thus coffee to wake up in the morning, and tea to relax in the afternoon, have a sound pharmacological basis.



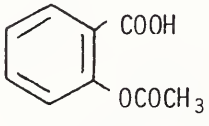
caffeine



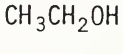
theophylline



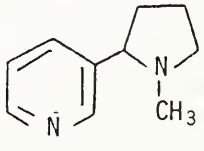
theobromine



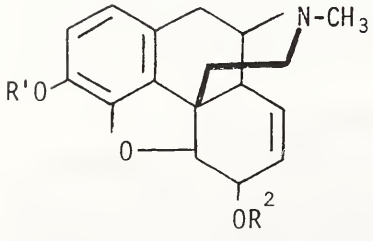
aspirin



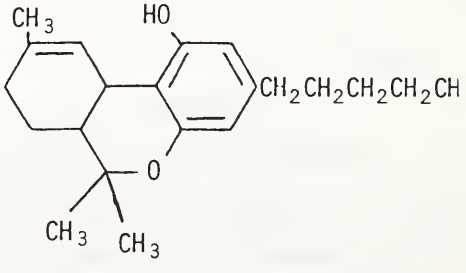
ethanol



nicotine



morphine, R'=R²=H
codeine, R'=CH_3, R²=H
heroin, R'=R²=CH_3CO



Δ'-3,4-*trans*-tetrahydrocannabinol

FIGURE 4.

Aspirin, or acetylsalicylic acid (Figure 4) is another widely used drug which has been shown to have mild CNS activity. While commonly used as an analgetic, or pain killer, it has many other activities. One of these is as a mild tranquilizer, actually counteracting the effects of the CNS stimulant tryptamine on the EEG of brain-canulated cats. Thus, for a tense and nervous person, "two aspirin and a nice cup of tea" is good medicine.

Another widely used drug is alcohol (ethanol, Figure 4). This is a very simple compound, and might be classified as a food, since its metabolism produces energy, and its carbon atoms are incorporated into body fat. However, it has various pharmacological activities, and has been used as a drug since ancient times. Alcohol is not a stimulant, as some believe, but is instead a depressant, and can act as a general anesthetic in high dosage. It was so used for surgery in early days. The apparent stimulation of the CNS, observed as the cocktail hour progresses from quiet clusters of friends at the beginning to noisy and boisterous behavior as the evening wears along, is in fact due to depression of the higher inhibitory brain centers, thus removing common inhibitions. Another effect of alcohol is vasodilation, causing a warm flushed skin. This can be beneficial to the angina sufferer, as it relieves the heart muscle, but heat loss is increased. Therefore consuming alcohol while out in the cold can be dangerous. Alcohol also stimulates gastric secretion at low concentration, but inhibits it at higher concentration. It is not always because the canapes are all gone that the late-stayers at the party quit eating and concentrate on drinking.

At 0.05-0. 10% blood alcohol, most people have a feeling of well-being, warmth of skin, and relaxation, with a loss of minor aches and pains. This blood level is equivalent to two to four ounces of 100 proof spirits consumed all at once. Another two ounces will raise the blood alcohol to 0.15%, at which concentration at least one half of the population will be intoxicated, that is loss of muscular coordination and slurred speech. Since the body ordinarily can metabolize about two ounces of 100 proof spirits in one hour, the wise drinker restricts the intake to no more than two drinks containing two ounces of proof spirits (the average cocktail) during the first hour, and no more than one drink per hour thereafter. He never drinks at the ball-game, rather waiting to dilate his peripheral vessels in front of the fire, where he can absorb the heat rather than lose it.

Nicotine (Figure 4) is another drug commonly used. It is highly active, and can be taken in small dosage by smoking. At low concentration, it has several effects. It is a central nervous stimulant, and increases heart rate and respiration. However, at high dosage, as by direct administration, these effects are reversed, resulting in mental depression, and paralysis of respiratory centers, resulting in death. However, continued use results in a high degree of tolerance. The compound is quite toxic: one cigar may contain enough nicotine to kill two men, if administered by intravenous injection.Two other ancient, but less commonly used drugs are the opium alkaloids (morphine, codeine and heroin, Figure 4) and the cannabanoid compounds found in hashish (*Cannabis indica*) and marijuana (*Cannabis americana*). These two classes of compounds have quite different effects. Opium was used for its sedative or narcotic effects, and the active principal, morphine, has valuable medical use as a powerful analgetic. Cannabis, on the other hand has no comparable medical benefit, and is generally used for its hallucinogenic properties. Its supposed beneficial effects on glaucoma have not been born out in tests with the pure active principal, delta-1-3-4-*trans*-tetrahydrocannabinol (Figures 4). The red oil, extracted fom both *Cannabis indica* and *Cannabis americana*, contains a mixture of geometric and stereoisomers, of which delta-1-3-4-*trans*-tetrahydrocannabinol is one of the more active. Synthetic homologs have been

prepared which are as much as five hundred times as potent as the natural extract. This drug has the effect of releasing inhibitions, but without effecting coordination. Currently there is much research investigating analogs and related structures, and a number of interesting leads to a variety of drug actions have been obtained. The value of marijuana may be in providing a molecular structure pattern which will lead to new classes of useful drugs.

In summary, then, we have seen that the availability of chemical compounds which can be used in humans can sometimes lead to new treatments of intractable diseases. Further, it was shown that minor molecular modifications, such as the introduction of a methyl group at a strategic location on a molecule, may lead to subtle differences in the biological activity of a compound. Finally we have shown that molecules with similar molecular structure frequently have related biological activity.

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