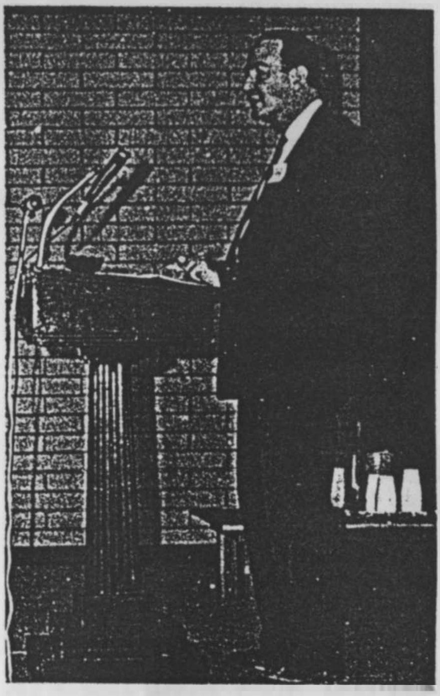
Biological roots of addiction are seen in the phenomenon of adaptation in nature and in genetic coding.

ONE way of improving our understanding of alcoholism is to look at its place in a wider framework. I propose to look at alcoholism as a specific case of drug addiction.

Alcohol is a drug like morphine or cocaine, peculiar in some ways, similar in others. Alcoholism shows all the characteristic properties of drug addiction. One can learn about it by reviewing the strange phenomenon that a human being can become dependent on the intake of a chemical substance, can commit an anti-social, criminal act to obtain the substance, can regard the drug as the most important part of his life, both an angel and a devil, to be praised and cursed,



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BIOLOGIC AND ADDICTIVE ASPECTS OF ALCOHOLISM

but hardly able to exist without.

Man and his reaction to drugs can be regarded from many different angles. For the purpose of understanding, one has to look at these angles separately—look at man as a biochemical machine, a physiological organism, an individual who behaves in reaction to surroundings according to inherited and acquired guidelines, a social and a religious one. In stressing the biological angle of man's

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addiction, it is assumed that everybody realizes that this is only one of many viewpoints.

One of the puzzling aspects of addiction is its compulsive nature: the addict has to take the drug again and again, increasingly threatened by the appearance of frightening withdrawal symptoms as soon as he is without drugs. Addicts frequently compare the way they feel in the absence of the drug with hunger; it feels "as if something were missing." "I feel normal after my injection, sick only without it," can be heard frequently. Sudden withholding of the drug can cause severe circulatory and autonomic nervous symptons, fall of blood pressure, change of heart rate, shallow respiration, goose pimples, diarrhea, etc. The withdrawn addict lies for several days moaning under his blanket, unhappy, depressed, weak.

On the other hand, the achievement of "normality" under drugs frequently requires the taking of increasing doses. De Quincy in "Confession of an Opium Eater" tells us that he finally had to take 133 drachms (about 300 times the therapeutic dose). In order to feel "normal" and comfortable an addict has to take an amount of the substance that would kill the unaccustomed. Do we know something more about this? Can we understand it better as a general biological phenomenon, or is this only the manifestation of an individual's mad search for pleasure?

A look at the phenomenon of adaptation in nature appears to be helpful. Adaptation is built into all living beings. It can be studied at any level of organization and is easiest to study at the level of animals with one cell.

Dr. Phillip B. Dunham, a biochemically oriented zoologist at Syracuse University, New York, observed such mono-cellular organisms in their normal surroundings, namely in tap water. The animals swam around, ate, propagated, and showed all the signs of healthy behavior. He then added some sodium chloride to the water in increasing amounts every day. As long as he kept the daily increase small, these animals lived "happily" in a 200 mm sodium chloride solution, the same solution which would have killed them if they had been put into it at the beginning. Another experiment showed that the little animals were no longer the same; when he transferred some individuals back into clear water they burst immediately and died. Only a gradual, slow reversion to original living conditions permitted the animals to survive.

Dr. Dunham, in trying to find out what the difference between the adapted and unadapted animals was, went a step further in his investigation. The normal animal of this kind tries to preserve a steady concentration of 12 mg per cent sodium on the inside. It achieves this with the help of a pumping mechanism with which it eliminates excess sodium or lets sodium in from the environment. The cells brought into the high sodium concentration at first accumulated much more sodium inside—105 mg per cent instead of 12 mg per cent. But soon their pump began to work faster, and the sodium concentration was brought back near control levels (to 21 mg per cent). This new level of pump activity could no longer be reduced on short notice, and the cell brought into the original medium died from lack of sodium inside. Only gradual reduction of sodium concentration outside permitted the pump to reduce its speed. The cell had adjusted to cope with the high sodium outside in the course of several weeks, and was unable to stand sudden reduction. I leave it to you to draw a parallel between these observations and the phenomena of tolerance and withdrawal symptoms in the addict who is, after all, another biological system in a chemically changed environment.

From the first model, the compulsiveness of the process becomes understandable. Whether there is much pleasure involved in obtaining the effect of the drug seems, at least at the later stage of addiction and after the development of tolerance, quite irrevelant. The fact that some drugs which cause a most interesting and frequently enjoyable experience like mescaline (from cacti) or psilocybin (from mushrooms) are not liable to produce addiction while others show a high addiction liability should have already made us cautious toward the conclusion that the individual seeks pleasure through repeated drug administration. It can be experimentally established that some drugs possess *a priori* a high addiction liability and others do not. What makes a drug this way is not known. Could it be that addicting drugs stimulate a certain area in the central nervous system, and that this area has to be stimulated again and again to obtain satisfaction, establishing a vicious circle, once the process has started? Experiments of James and Marianne Olds in Michigan seem to pinpoint such a center.

Experiments Conducted

These experiments managed to implant in a number of rats two electrodes in different areas of the brain. Each pair of electrodes was connected by means of wires to an electronic stimulation device above the cage, the wires being designed in a way which did not restrain the animals in their movements. The Olds' built a lever into the circuit which could be pressed by the rat; each pressing would release a series of small electric stimuli of one half second duration. If the lever was held down, or if it was released and not pressed again, no stimulation would occur. The experimenters wanted to find out whether such stimuli would be perceived and manipulated by rats in a way that would reduce stimulus frequency to a low level. A recording device indicated the amount of stimulation that the rat had produced over a certain period of time.

The surprising discovery, which has since been confirmed by many investigators, was that when the electrodes were placed in such a way that certain areas in the forebrain system were stimulated, the animal quickly learned to press the lever very frequently. Rates (in eight minutes) ranged from 600 up to 1200 responses and higher. All other areas showed the rats either carefully avoiding restimulation after one effort, or the animals were indifferent.

To clarify further the nature of this effect, Olds and Olds compared the rewarding nature of the stimuli with those of eating in hungry animals. Instead of food as reward, self-stimulation was used to cause organization of a complicated response pattern like learning to run through a maze. When two groups of rats were compared, one receiving food as reward for crossing the maze and the other receiving self-stimulation, both learned equally fast to reduce mistakes. However, the stimulation group ran faster for the reward than the hunger group. When, after four days of training, the stimulation reward was withdrawn, extinction of the acquired response appeared with the same speed for both groups in about four days. These observations appear particularly interesting in the light of the frequently quoted remark by addicts that drug withdrawal is like getting hungry, and the drug makes them feel satiated. But notice that in these experiments no drugs were involved.

Let us return to drugs, but stay with our animal models for the purpose of obtaining further insight into the self medication and regulation of dosage. The experiments to be described in the following were carried out by J. R. Weeks in rats and monkeys. They chose settings in which rats could take the drug at will, regarding this as a model relatively close to the human addict.

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For the purpose of their investigation a tube was positioned in the rat's heart and connected to a syringe. The syringe, outside the cage, was pushed forward by a motor to inject a measured standard amount of fluid as soon as the rat pressed the lever. In the beginning of the experiment, the rat received a shot of morphine every hour for two days, starting with 2 mg and building up to 40 mg per kg. At the end of the second day the mechanism was adjusted so that the rat could inject itself with a 10 mg dose of morphine each time it pressed the switch. Most rats stabilized thereafter at one injection every two hours—some a little more frequently, some less. They were apparently able to gauge the desired dose.

The next step in the experiment was taken to find out how well the rat would be able to adjust the dose if conditions were changed. Instead of 10 mg/kg morphine per injection, the solution was diluted to deliver 3.2 mg/kg each time the lever was pressed. In a few trials the rats established a new rhythm, injecting themselves now about twice as frequently as before. If morphine was further reduced, injections grew even more frequent. And leaving out morphine from the solution altogether, a high frequency injection pattern was followed by slowing down to almost cessation of lever pressing. All abstinence symptoms could be observed in the rats, and the symptoms could be promptly relieved by a single injection of morphine.

The mechanism could be programmed to inject a single dose of morphine only after ten lever pressings. The rats reacted with keeping quiescent in the intervals and pressing 10 times in a row at the end of two hours, so that the original dose per time was received—indicating again the ability to titrate the optimal amount. Replacement of morphine with other addicting drugs showed the same pattern of response.

A last set of animal experiments should be discussed now because they shed light on the role of differences in different individuals. On closer observation it becomes apparent that some persons do not become addicted to drugs in spite of extensive exposure, while others seem to seek out the places and surroundings where drugs can be obtained and are used. It is very difficult to separate the role of the early experience of a person from that of his inherited traits. Though it seems likely that addiction in parents makes children more susceptible to similar behavior, we hardly know how much of this is due to early influences and how much is inescapably anchored in the genes. Another question that the following experiments try to answer is that of the choice of drugs. Can a certain person or personality become addicted only to a certain drug, or is drug selection a question of more or less accidental exposure?

Just last year two investigators, Nichols and Hsiao, published the results of a series of experiments in *Science* which, I believe, shed some light on these questions. They caged rats individually and offered two calibrated 100 ml drinking tubes—one with tap water and one with 0.5 mg morphine per ml water. Rats automatically preferred the water and never touched the morphine solution, even after they had been injected with morphine once per day in the amount of 10 mg/kg for 17 successive days. However, if the rats were deprived of water for 24 hours, then received only morphine solution to drink for 24 hours, then they got tap water for another 24 hours, and if this was repeated 5 times for altogether 15 days, they preferred the morphine solution to water. When the morphine solution was withdrawn, three days of severe withdrawal symptoms appeared; 12 days later animals were close to normal and no longer showed signs of physical dependence. At this time rats were brought into the original situation in single cages with tubes of 100 ml drinking water and 100 ml morphine solution to choose from. Soon some animals now drank regularly large amounts of morphine solution, while others drank little and preferred water.

After morphine preference had been established as a stable trait in certain individuals, the rats were separated into two groups—those that would prefer morphine over water and those that would rather drink large amounts of water. Animals in the middle range—which drank equally from both solutions—were eliminated. The morphine-drinking rats were now bred to each other and the water drinkers were also bred to each other. The morphine preference of the offspring was then tested. This procedure was followed through four generations. It could be established that the morphine preference increased from generation to generation in the one group and decreased in the other. The difference from generation to generation was increasing significantly below the 0.005 probability level.

After having established this preference pattern in the animals, the authors asked the question whether the preference of morphine over water was specific for morphine in each strain or whether it was a rather general drug preference. Again two strains of rats were used which had now been bred for four generations and they were tested for their preference for alcohol in water or clear water. It was again necessary to proceed through five periods of alcohol exposure in the way described above; one day of complete withdrawal of drink, one day of exclusive exposure to alcohol water, and one day exposure to tap water. At the end of this period the rats were again given a choice between the alcohol + water and clear water. It may be useful to remember at this point that previously rats would not have drunk water with alcohol at all; they apparently found this quite distasteful. It became quite clear that the morphine rats now became addicted to alcohol. After successful withdrawal, the morphine susceptible strain of rats drank twice as much alcohol as the other strain (24 vs 12 ml), and this difference was significant at the 0.005 probability level. Non-addictive drugs were not found to be preferred over water by any of the animals.

It is time to summarize what we have learned from the animal experiments. Let me repeat that we have only touched on a small sector of the problems which are related to drug addiction. No mention has been made of the preference for certain drugs in certain parts of the world: alcohol in the West and opium in the East. Little has been said about personality traits of the addict, his early experience, the exposure and opportunity to obtain the drug, his mental and physical health. We have also taken the liberty of lumping drug addiction together into one big category in spite of the fact that we know very well that one drug may stimulate the addict, another may make him sleepy, another —like alcohol—acts first one way and then the other. This was done to draw a more general picture of the biological roots of addiction, certainly a simplified one, but one which is important and impressive.

All experiments have clearly indicated the compulsive nature of drug addiction at the cellular level, in brain stimulation, or in self medication. Once started, the deviation, or adaptation, grows according to its own laws. The development of tolerance, or adaptation, and the causally related withdrawal symptoms force the addict to continue drug self medication with increasing doses. For some unknown reason tolerance to the undesirable effects of the drug frequently develops not at the same rate as tolerance to its desired effect, and the addict gets increasingly uncomfortable. Once "hooked," he looks no longer for a pleasurable experience or "the shortest way to paradise on earth," he just wants to feel—in his own words—"normal." Independent of whether we attribute freedom of will and moral responsibility to man, the observation that an animal can be bred to high or low drug preference is a biological argument in favor of regarding the addict as a person severely afflicted, rather than as somebody with evil designs.

But in reading newspaper articles and even some of the professional journals, one cannot help getting the impression that addicts are sometimes considered as people who have only to be severely reprimanded or even threatened with punishment and they will pull themselves together and break the habit. The deep roots of addiction in biological properties of adaptation and in genetic coding contradicts the reasonableness of such an attitude.

The results of the experiments just quoted together with much other evidence seem to me to teach us another lesson: to put all the blame on the drug appears to be too easy a way out. Remember the rats which became "addicted" to an electrical stimulus in the brain and preferred this as a reward over food? Remember the animals which showed high morphine preference but then manifested a similar preference for alcohol? I propose that we regard the drug as only an instrument; it can be used in many ways, skillful or clumsy, for good or bad, depending on the hands of the user. The instrument can easily be exchanged, but it is the guiding hand that makes it useful or damaging. Biological thinking warns us not to get too satisfied with pointing to alcohol, morphine, or LSD as the source of trouble. We should rather treat sick individuals and a sick society if they are found to misuse a drug.

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tractual basis and is under the direction of Harold Holder, Ph.D. from the Department of Mental Health. The program planning and implementation will be determined by a regional team, consisting of representatives from each of the nine mental health areas, the regional director and staff from Dorothea Dix Hospital, with consultation from the Department of Mental Health and the above resource persons.

As a summary, the South Central Regional Alcoholism Program, through an application of systems analysis, is to look at alcoholism and alcohol related problems of the region to determine if existing methods are inadequate. If so, what alternatives are there, how can they best be implemented, and what would they cost, and what are their predictable consequences.