The New York Times

A Kansas pot field. Potency varies from plant to plant and country to country.

MARIJUANA

Pot facing stringent scientific examination

by Barbara J. Culliton

To cool the heated controversy that surrounds marijuana, parents, Congressmen and even the medical community are calling for some definitive word on the pros and cons. What is wanted is something in the nature of the Surgeon General's 1964 report on smoking, which laid out the hazards in exhaustive detail. Immediate action is being demanded.

In the Senate, Peter H. Dominick (R–Colo.) has already introduced a bill requiring an annual report to Congress on the current status of biomedical knowledge, including recommended legislation. In the House, Rep. William E. Minshall (R–Ohio) has proposed a similar bill.

It is an ambitious demand.

Progress reports on marijuana research are possible. The definitive biomedical statement the proposals seek is not. Not enough is known yet (SN: 9/27, p. 263).

For all that has been said and written on marijuana, little is founded on a firm scientific base. In spite of man's long history of pot smoking—records of its use date at least to 2737 B.C. when it was listed in the herbal compendium of the Chinese Emperor Shen Nung—the chemistry and pharmacology of the active ingredients of the cannabis plant have attracted only slight research attention. Fact and folklore regarding its effects remain to this day virtually inseparable.

But distinctions are in the offing. In the face of prevailing concern over the mushrooming use of pot in the United States, and its possible medical and so-

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Research and the law

In the relations between science and Government, it is the role of research to provide the insights into natural processes that legislators and administrators need in the shaping of national programs.

Once the basic research has been done, the search among known facts for appropriate avenues of approach may be relatively easy. But there are subjects about which little or no valid research has been done and few hard facts are available, but which involve such pressing social issues that national leaders must turn to science for guidelines.

Marijuana is such a subject. It is tied in the public—and legislative—mind to the alienation of a generation, opposition to national domestic and military policies and the outbreaks of violent dissent that appear to defy explanation in conventional terms. It is a focus of increasing social concern.

Unfortunately, in light of the intensity of the search, the appeal to science for answers at this time is a fruitless one.

Marijuana is not a subject about which a good deal of research has been done. Unlike cigarette smoking, it cannot be approached by way of a Surgeon General's report, sweeping up a vast body of knowledge and pointing the way to an intelligent public policy.

Research is only starting, and answers are only beginning to evolve.

It is significant, then, that the original, repressive tendency of the Nixon Administration in relation to marijuana has been tempered by the concern of scientists and others for a less punitive approach.

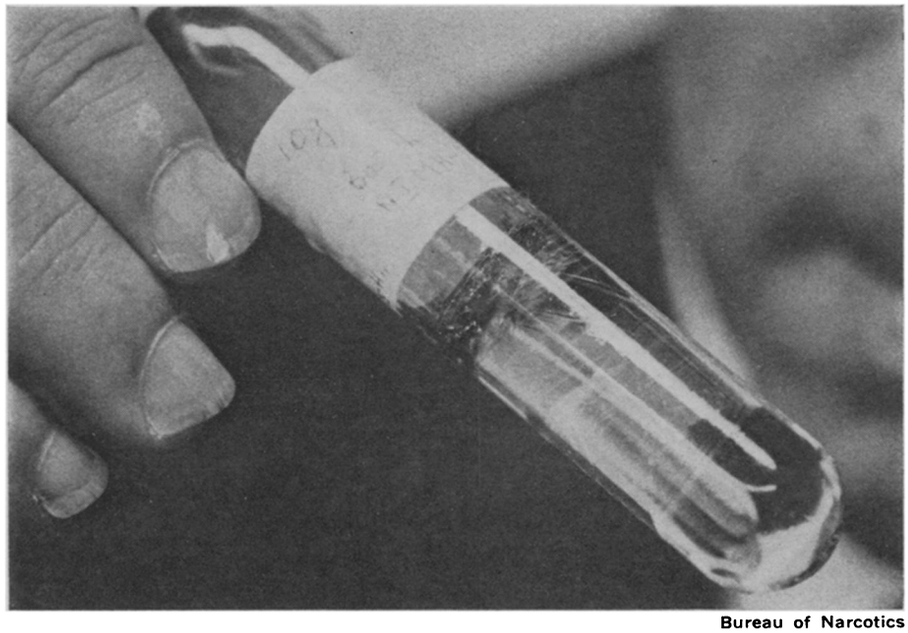
And it is equally significant that the legislation presently proposed (SN: 10/25, p. 371), already approved by the Senate Committee on the Judiciary and expected to be enacted early in the current session of Congress, contains a provision empowering the Government to change its mind.

While differentiating marijuana from heroin, the bill contains a provision enabling the U. S. Attorney General to reclassify the drug later, as information about it is developed.

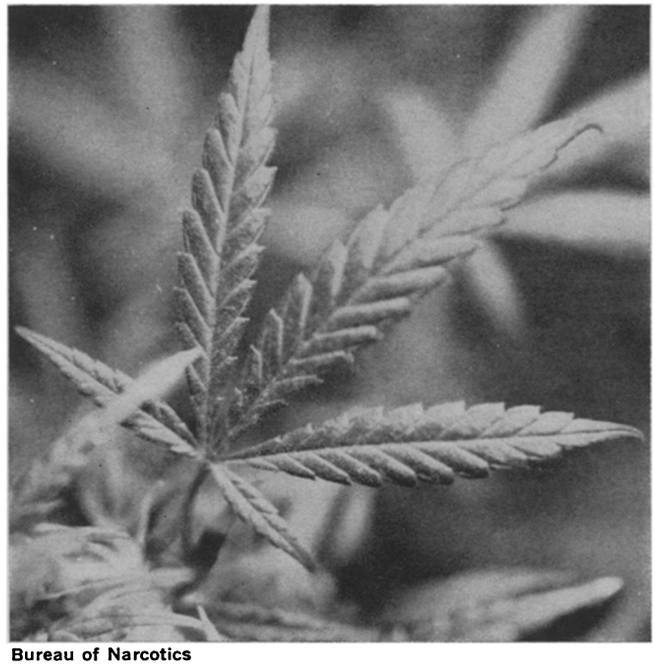
At the same time, the determination of Federal officials to develop the information they need to deal intelligently with marijuana is taking the route of increased support of research.

The article that begins on this page explores the pharmacological and biochemical research growing out of the current concern over marijuana and the insights that are beginning to develop. In a subsequent issue, the editors of SCIENCE NEWS will deal similarly with the level and nature of the social and behavioral research also being stimulated.

The first concerted effort at defining the biological effects of natural and synthetic marijuana is under way with Federal support



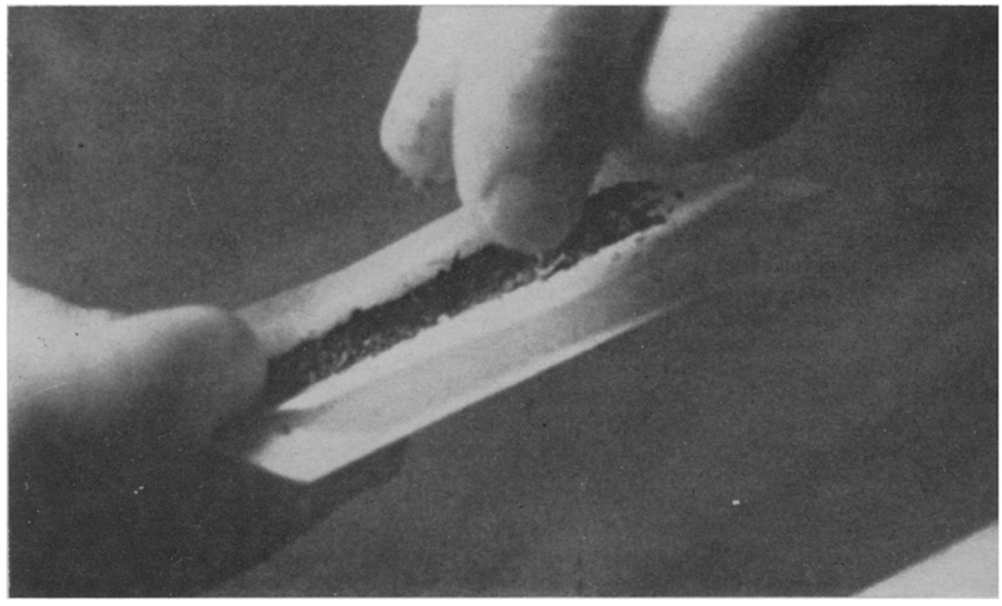
Bureau of Narcotics



Bureau of Narcotics

Investigators will compare the effects of natural marijuana from the cannabis plant (center) with synthetic THC (top).

NIMH



cial consequences, marijuana research is being approached with an unprecedented sense of urgency. Dr. Stanley Yolles, director of the National Institute of Mental Health, has promised Congress answers within two years. While not all marijuana researchers share his optimism, virtually everyone involved concedes that there is enormous pressure to get things moving and come up with data soon.

To this end the Government, through the NIMH, has invested nearly $10 million. As of April, 67 projects in the biological, social and psychological sciences were approved for funding, though most are only now getting under way.

The delay, and the flaw in what previous work there is, rests with the lack of good marijuana for study. The essence of an experiment is the reproducibility of its results. Until last fall, this was virtually impossible because no two scientists could be sure they were testing the same chemical.

By and large, tests have been made with material extracted from marijuana confiscated by the Federal Bureau of Narcotics. Because methods of extracting pure chemicals from the raw plant are not standardized, and because the quality of chemicals varies from plant to plant, comparisons of various results have been relatively meaningless. Foreign data, too, have little applicability because European and Asian marijuana is generally more potent than its counterpart from crops grown in the United States.

To eliminate this deficiency, two

types of projects were initiated. At the University of Mississippi, where scientists have $115,000 in NIMH money, marijuana is being grown. Comparative studies will be made of plants from various parts of the world in an effort to define the chemical characteristics of cannabis compounds and to determine relative degrees of potency.

Standardized crops are also being developed. "Only now," says Mississippi's Dr. Coy Waller, "are batches of drug from these plants becoming available." They will be released to investigators through a special NIMH panel that meets every three months.

The second line of attack focuses on the preparation in the laboratory of two of the active constituents from the female cannabis plant—delta 9-THC (tetrahydrocannabinol) and delta 8-THC. In nature the former appears to be the primary active ingredient, since only very low levels of the delta 8-THC molecule have been isolated from cannabis. Contracts for the THC synthesis have been issued to the Arthur D. Little Co. in Cambridge, Mass.

Synthesis of crude THC is relatively simple. As one chemist puts it, "You can make it in the bathtub." But producing the large quantities of pure delta 8-THC and delta 9-THC for research in animals and for clinical study is another matter. According to Dr. Harry Pars, Arthur D. Little chemists have spent a year ironing out problems in the synthetic process, which involves the same requirements for quality control and large-scale production that major drug houses face.

Supported by NIMH contracts of approximately $150,000, the company will make about 2.5 kilograms each of delta 8-THC and delta 9-THC, to be released only through the NIMH.

"At this point," Dr. Pars says, "we have produced more than half of the total amount. The delta 8 is 98 percent pure or better and we believe we can approach that purity with the delta 9, which is about 90 percent pure now." The current supply should meet research needs in laboratory animals for a couple of years, since doses used are relatively small. A marijuana cigarette containing 500 milligrams of material would be at most one to two percent delta 9-THC.

Pure THC, made from ingredients that chemical and drug companies are becoming increasingly careful about selling, is a highly viscous material that looks like dark molasses. Highly insoluble in water, it must be mixed with a solvent for injection and is not well absorbed when taken orally. It appears to degrade or decompose with time, and is best handled by sealing it under nitrogen and storing it at lower than room temperatures.

In another project, at the Research Triangle Institute in North Carolina, chemists are concentrating on the synthesis of radiolabeled delta 8-THC and delta 9-THC. They plan to produce up to five grams under an $85,000 contract, also from NIMH. At the same time they are working to perfect methods of extracting red oil from marijuana plant material confiscated by the Narcotics Bureau, as a guide to extracting standardized compounds from freshly grown plants. "Red oil," says Dr. Munroe Wall, director of the chemistry and life sciences division, "is a semi-pure concentrate, a dark reddish-brown in color, which can be obtained in large amounts and is representative of the whole plant. About 20 percent of red oil concentrates is delta 9-THC."

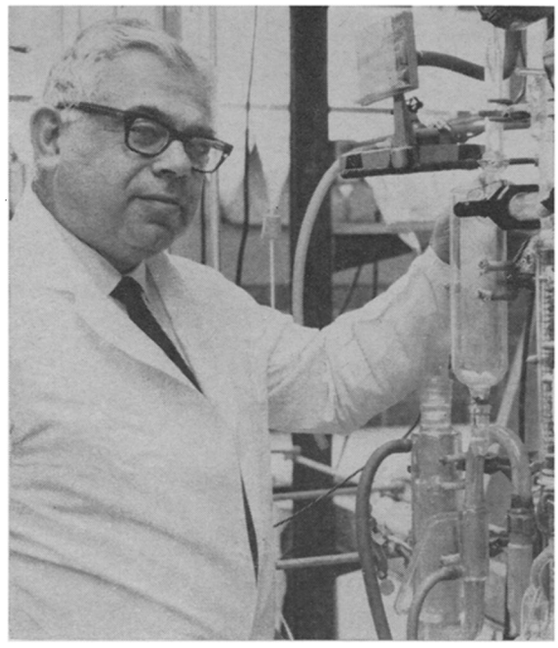
With these materials in hand, scientists are turning to basic studies in the pharmacology, toxicology and biochemistry of marijuana. First in animal studies and then in man, they are comparing the natural and synthetic compounds, examining the nature and effects of components in the natural material other than THC, and studying the fate of all of them in the body.

Dr. Wall and his co-workers, for example, plan long-term toxicity studies with red oil and will use radiolabeled THC in studies of metabolism and biological distribution.

Though studies are just beginning, some information is available. In one case, for instance, he finds that fatty acids are associated with delta 9-THC in some extracts. "This may not be typical of all natural marijuana," he says, "but it is true of material confiscated from Mexico." In a second Research Triangle project aimed at determining where the drug goes in the body and how it is handled, there is preliminary evidence identifying one of the metabolites or breakdown products of THC. "Now we want to see if this metabolite has biological activity or toxicity," he says.

Limited studies of THC in mice at the University of Chicago have yielded some data about its effects on brain chemicals, though, Dr. Richard A. Lovell asserts, "It is far too early to draw any conclusions from our work about marijuana's effects on behavior." THC clearly releases behavior-affecting catecholamines into the blood, but explanations of its metabolism in the brain await further experiments.

Other researchers also have preliminary data. Says Dr. Robert Schlant of Emory University in Atlanta, "There is reasonably good evidence that marijuana causes tachycardia (a rapid beating of the heart) but the mechanism is unknown." Now awaiting his supplies of THC, he expects to explore this phenomenon in animal studies by sewing gauges to the surface of dogs' hearts and then injecting THC to measure its effects.



Research Triangle Institute

Dr. Wall extracts red oil fractions.

Also awaiting supplies of THC is Dr. Eugene Boyd of the University of Rochester. He intends to conduct experiments with squirrel monkeys to trace the pathways THC follows to the sensory areas of the brain, in an effort to determine its effects on perception.

At the University of Mississippi, Dr. Henry Pace is beginning animal studies of marijuana's possible teratogenic effects—there is some evidence it crosses the placenta and enters the fetus—and in Massachusetts, at the Worcester Foundation for Experimental Biology, Dr. Sumner Burstein is using radiolabeled THC in rabbits to examine metabolism (SN: 9/27, p. 263). His work, like that of Dr. Wall, indicates a THC metabolite may be an active component.

When these and similar projects show results, it will be possible to describe marijuana with greater precision. At present, the most one can say about it with reasonable certainty is that it is not addictive in the way narcotics are—that is, it does not lead to physical dependence characterized by withdrawal symptoms—and that its possession by anyone other than an approved researcher is illegal.

Research into the chemistry and pharmacology of marijuana is not all designed to fill gaps in existing knowledge. Some scientists are directing their attention to possible therapeutic uses of synthetic drugs that resemble THC. Chemically, THC is not like any other known class of compounds. Unlike most compounds derived from plant

extracts and active in the central nervous system, THC contains no nitrogen. According to pharmacologist Dr. Louis S. Harris of the University of North Carolina at Chapel Hill, classic drug-study tests are not always applicable to THC. And, he says, though its mode of action is not fully known, it exhibits "a mix of both stimulatory and depressant activity on the central nervous system."

In projects during the last few years, Arthur D. Little chemists have synthesized a number of new classes of compounds that are molecularly like THC but which, Dr. Pars stresses, are not marijuana.

"THC has not been carefully studied heretofore for its effects as a potential drug," he states. Nevertheless, compounds synthetically derived with its molecular structure in mind may be useful.

He lists three areas in which chemical and animal experiments are under way:

- Analgesia: Some of the new compounds exhibit definite effects in some of the animal procedures designed to screen and evaluate pain-relieving drugs. These new agents appear to be similar to mild mood elevators as well as to analgesics, and this combination could make them unique and potentially useful drugs.
- Blood pressure reduction: Some scientists postulate a form of hypertension that is related to environmental circumstances, unlike forms induced by organic or physiological changes. Among the new agents are some that appear to lower blood pressure by biological mechanisms at present unknown but possibly acting through the central nervous system.
- Psychotherapeutics: Again, preliminary evidence indicates that certain of the new compounds, in various pharmacological profiling procedures, act as antidepressants and antianxiety drugs by a mechanism unlike those of available agents.

Considerable animal work remains to be done on these agents before it will be possible to define their therapeutic activity with precision, and it may be a matter of a few years before they can be candidates for the necessary initial trials in man.

The extent to which laws and attitudes to marijuana will be affected by the outcome of scientific investigation remains to be seen, but researchers contend that without the body of information they are accumulating there will be no possibility of reaching rational positions. The present situation, they agree, is founded simply on ignorance. □