the opportunity to study the emergence of collective rotational motion in a system with few degrees of freedom. In such a situation, the problem of identifying the spurious particle-degrees of freedom—those out of which the rotational motion is formed—becomes especially acute.

The behavior of the rotational bands for large values of the angular momentum constitutes a frontier of vigorous activity. The current developments involve the problem of the limit of convergence of the power series expansions in the rotational frequency or angular momentum and of the many types of discontinuities that may occur in the bands for large values of the angular momentum when the rotational forces distort the nuclear structure in a major way. Some of these discontinuities may resemble phase transitions in macroscopic systems, and, in the nucleus, it may become possible to follow such transitions in terms of the properties of the individual quantum states. For the very large values of the angular momentum that can be transferred to a nucleus in an impact with a heavy ion, we encounter nuclear matter in a hitherto unknown form.

Epilogue

The development of nuclear physics in the past decades has been characterized by the great richness of the phenomena that have been encountered, and I have tried to describe a few of the concepts that have been involved in the attempt to understand these phenomena. Looking ahead, one can already see great new areas that may be explored by means of the new tools that are becoming available, and one can look forward to the inspiration which this expansion of our horizon will provide for the refinement and further development of concepts for the description of quantal phenomena (*3*).

Notes

1. For an account of C. C. Lauritsen's scientific work, see the biographical memoirs by W. A. Fowler in the *American Philosophical Society Yearbook* (1969), p. 131. The early development of nuclear research at California Institute of Technology is also vividly described by T. Lauritsen in the special issue of *Eng. Sci.* 32, No. 9 (June 1969) published by the California Institute of Technology.
2. The development has been the result of a lively interplay of evidence and ideas coming from so many different sources that it would fall outside the scope of this presentation to attempt to mention the individual contributions. A more detailed account, with inclusion of references to the main steps in the development, has been prepared in another context, in collaboration with Ben R. Mottelson.
3. The lecture concluded by a comment on the proposed establishment of an International Science Foundation. The idea of channeling part of the resources available for scientific research through such an organization arises naturally in view of the international character of science. An International Science Foundation will be able to base its functioning on the existence of an international community of scientists who by and large share the same standards and goals for scientific research and will be in a position to evaluate research projects in an international perspective. It will be a primary task for the Foundation to help ensure that scientific talent and initiative, wherever in the world they appear, can contribute to the progress of science and, in this spirit, the Foundation might be of considerable value in promoting science in the developing countries. Plans for the establishment of an International Science Foundation were discussed at a meeting in Stockholm in July 1970, sponsored by the Royal Swedish Academy of Engineering Sciences, the Royal Swedish Academy of Sciences, Unesco, and the American Academy of Arts and Sciences, and are at present being studied by an interim committee set up at this meeting.

Marihuana in Man: Three Years Later

Mental and physical effects have been confirmed, but their causes and implications remain uncertain.

Leo E. Hollister

Few drugs have been used so long and by so many people as that derived from *Cannabis sativa*. Until the spectacular resurgence of use of marihuana by Western society during the past decade, scientific interest had been largely dormant. During the past 3 years, in particular, this interest has been rekindled, in part because of the social importance of the drug, in part because of the possibility of doing more precise studies, and in relatively small part because research funds became available. After a slow start while legal hobbles were being ameliorated, the rate of increase in scientific inquiry into the effects of marihuana has risen in almost an exponential manner. It may soon be impossible to keep current with the rapidly growing literature. It seems propitious, therefore, to assess accomplishments in regard to marihuana's effects in man during the past 3 years, comparing these with those of the past, as well as taking inventory of what still needs to be done.

Marihuana in Man: Past

Customarily, those of us engaged in research with marihuana deplore the ignorance that existed about the drug before we came along. Much of the work of the past, to be sure, was based on descriptions of effects by individuals exposed to uncertain doses of the drug. Still, much of the newer work with marihuana involves the rediscovery of phenomena known for a long time, sometimes camouflaged by coining new names for old phenomena or by elegantly proving the obvious. Looked at in its historical context, the present flurry of experimentation may have contributed less that is really new than we like to believe.

Baudelaire, an avid member of the hashish cult fashionable in Paris during the middle of the 19th century, provided an elegant description of its clinical effects. He may either have used more than a little poetic license or have taken enormous doses of the drug (*1*). If we brush aside much of his rhetoric, we find that he clearly described such phenomena as euphoria, uncontrollable

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laughter, paresthesia and weakness, perceptual disorders affecting time, space, and hearing, mental disorganization with flight of ideas and incoherence, hallucinations, and depersonalization. His account of his experience with hashish is strongly reminiscent of later accounts of the effects of psychotomimetics. That higher doses of the drug were psychotomimetic was recognized by his contemporary, the psychiatrist, Moreau de Tours, who not only took the drug himself, but encouraged its use by his students so that they could gain insights into mental disturbances (*2*).

Similar descriptive accounts, which have hardly been improved upon today, are found in the monograph by Lewin: Anxiety and restlessness; euphoria; hilarity; faintness and weakness; perceptual distortions; flight of ideas and mental confusion; and finally, sleep. Like effects of the drug are described in two reports from India, both of which were primarily concerned with sociological questions revolving about the widespread social use of the drug (*3*).

Concern about the social use of marihuana in the United States stimulated some investigations in the early 1940's under the auspices of the La Guardia commission (*4*). These were quasi-pharmacological studies in which measured quantities of marihuana were both orally administered and smoked. Measures of dose were usually in milliliters of an alcoholic extract of marihuana or milligrams of marihuana leaves, both of unknown composition, so that pharmacologic precision was somewhat illusory. Effective doses were obtained, however, and clinical effects resembled those described before. As always, euphoria was prominent, as was difficulty in concentrating or maintaining attention; floating sensations or feelings of heaviness and lightness; dryness of mouth; blurring of vision; palpitation and tachycardia; and increased appetite. Laboratory studies were usually within normal limits. Electroencephalographic studies were thought to show a correlation between euphoria and increased alpha activity. Performance tests, such as static equilibrium, hand-steadiness, tapping speed, and complex reaction time were impaired. Users of the drug were more tolerant of impairment and less likely to experience initial anxiety or excitement than were nonusers. Tests of various intellectual functions showed some impairment at higher doses, but many tests remained unimpaired by the modest doses used. The wavelike character of the syndrome, with waxing and waning, as well as the development of frank hallucinations in some subjects, was noted when somewhat higher doses were used. Studies of a synthetic homolog, synhexyl, revealed similar findings (*5*, *6*).

Thus, by the late 1950's, many of the phenomena of marihuana intoxication had been described. It was not until another 10 years had passed and a marked change in the patterns of use of the drug had occurred in American society that interest in clinical studies was again revived.

Marihuana in Man: Present

The availability of synthetic *trans*-Δ^1-tetrahydrocannabinol (monoterpinoid numbering system; tetrahydrocannabinol is henceforth referred to as THC) as well as chemical techniques for quantifying its content in marihuana has made possible for the first time pharmacological studies which provide some precision in dose (*7*). When the material is smoked, a still uncertain and variable fraction of THC is lost by smoke escaping into the air or exhaled from the respiratory dead space. Relatively little is lost by pyrolysis, as it is likely that the cannabinoid is volatilized in advance of the burning segment of the cigarette. The efficiency of the delivery of a dose by smoking has been estimated from 20 to 80 percent, but with most experienced smokers it should approximate 50 percent (*8*). Synthetic THC and marihuana extracts are also active by mouth, but doses equivalent in effect to those from smoking are about threefold larger (*9*). Undoubtedly, some THC may be inactivated within the gastrointestinal tract or during its passage through the intestinal mucosa and liver. As no method for the quantitative estimation of THC concentration in plasma or urine is available with usual chemical techniques, the actual doses of THC obtained by various routes are still unknown.

When smoked, THC is rapidly absorbed and effects appear within seconds to minutes. If marihuana is of low potency, effects may be subtle and brief (*10*). Seldom do they last longer than 2 to 3 hours after a single cigarette, although users prolong effects by repeated smoking. Oral doses delay the onset of symptoms for 30 minutes to over 2 hours. Because synthetic THC, as well as marihuana extracts, requires nonpolar solvents, even the administration of accurate doses to animals for pharmacological studies has been a problem. Intravenous doses of drug are preferable to intraperitoneal doses in animals, as the latter may be poorly absorbed.

Because of the dual route of administration, as well as the still unsettled problem of whether natural marihuana materials have activity different from synthetic THC, we shall consider each type of clinical study separately. Very likely most pharmacological activity is determined by the quantity of THC, the main difference being the route of administration.

Studies of Oral Doses of Synthetic THC: Three groups including our own at Veterans Administration Hospital, Palo Alto, have now published on the effects of oral doses of synthetic THC in man. The group at the Addiction Research Center, U.S. Public Health Service Hospital, Lexington, Kentucky, employed doses of 10 to 30 milligrams, or 120 to 480 micrograms per kilogram of body weight. We used doses of 30 to 70 milligrams, or 341 to 946 micrograms per kilogram. A group from the National Institute for Mental Health (NIMH) used a single dose of 20 milligrams, not specifying the weight of the subjects. Between the three groups, however, a rather wide range of dose was explored (*9*, *11*). It should be emphasized that, even if we account for the lesser potency of the material when given orally as compared to smoking, most doses were beyond those which might be obtained from smoking an ordinary marihuana cigarette. If one assumes that an average cigarette may consist of 500 milligrams of marihuana containing 1 percent THC and that delivery is 50 percent efficient, the dose delivered would be 2.5 milligrams of THC, equivalent perhaps to 7.5 milligrams of THC given orally. The experimental doses might be more comparable to those obtained from smoking several cigarettes of reasonable quality, or from smoking hashish.

1) *Physiological effects:* No changes in pupil size, respiratory rate, or deep tendon reflexes were observed. We found no change in oral temperature of any consequence, but the NIMH group reported a slight but consistent decline. All observers have commented on the constant increase in pulse rate, often one of the first effects of the drug. Blood pressure tends to fall slightly or remains unchanged; at higher doses, we observed

two instances of orthostatic hypotension. Conjunctival reddening is also constantly observed, and in this case is clearly not an artifact produced by irritation from smoke. Both this symptom and the increased pulse rate correlate quite well in time with the appearance and duration of psychic effects of the drug. We measured muscle strength with the finger ergograph and could demonstrate muscle weakness objectively.

2) *Perceptual and psychic changes:* Euphoria was most pronounced in our subjects, who were graduate students. It was less marked in the Lexington series, which used imprisoned former drug addicts, or in the NIMH group of subjects, who were prisoners at a correctional institution. Sleepiness was constantly observed, and often deep sleep followed the higher doses. Time sense was altered, hearing was less discriminant, vision was apparently sharper with many visual distortions. Depersonalization, difficulty in concentrating and thinking, and dreamlike states were prominent. Many of these symptoms were similar to those produced by psychotomimetics such as lysergic acid diethylamide (LSD), mescaline, or psilocybin. On self-reporting mood scales, our subjects became more friendly initially, but less so with the passage of time; less aggressive, especially late in the course; less clear-thinking persistently; sleepy, especially after 3 hours; euphoric persistently; and dizzy persistently. The NIMH group found only increased sleepiness and less clear-thinking with the same scale, but their comparisons were made against controls who received placebos rather than against their own baseline and were ratings by others rather than by the subjects themselves.

3) *Psychometric tests:* We used repetitive psychometric tests of arithmetic ability or freehand drawing, both of which were impaired in different ways. The arithmetic test, a familiar and simple task, showed a slowing of performance against time, with maintained accuracy. The drawing test, less familiar and more difficult, showed reduced accuracy with no slowing of performance, probably indicating some loss of finer judgment. The NIMH group found that accuracy of serial addition was impaired, but that the drug had no effect on ability to count backwards, to say the alphabet, or to repeat digits forwards or backwards.

4) *Biochemical tests:* We were the only group to attempt these measures. Amounts of free fatty acids in the plasma remained unchanged, unlike the case with drugs such as LSD where sharp elevations are observed. Glucose concentrations in the blood were also unchanged, despite previous reports indicating that marihuana produces hypoglycemia. The lack of change in plasma glucose values has now been verified on numerous occasions. Both creatinine and phosphorus clearance were temporarily decreased, a phenomenon which has been observed with LSD (*12*).

5) *Comparisons with other THC homologs and other materials:* We compared synthetic THC with the synthetic Δ^3THC homolog, synhexyl, both given orally. The latter compound has been studied rather extensively for possible clinical utility (*6*, *13*). On the whole, the changes reported above were also produced by synhexyl, but synhexyl was approximately one-third as potent as THC. The onset of the effects of synhexyl were delayed by about 1 hour, but lasted longer in equivalent doses.

The Lexington group compared the effect of taking THC orally with its effects when smoked (known quantities were added to cigarettes). They estimated that potency is increased approximately threefold by smoking as compared with taking the same material by mouth (*9*). As might be expected, effects appeared sooner, but were of briefer duration, when the material was smoked. They also compared the effects of smoked THC (75 to 225 micrograms per kilogram) with those of LSD given intramuscularly in doses of 0.5 to 1.5 micrograms per kilogram (*14*). Subjective effects between the two drugs were not readily distinguished, but objective differences were marked: LSD elevated body temperature, increased systolic and diastolic blood pressure, and exaggerated deep tendon reflexes and dilated pupils whereas THC had none of these effects. We made a retrospective comparison of the effects of LSD and THC taken orally and came to similar conclusions regarding the objective differences (*15*). Subjectively, we thought that THC produced less total impairment with more euphoria and dreamlike states than did LSD at comparable doses and that, unlike the latter drug, sedation was a prominent feature with THC, with most subjects falling asleep. In general, we have seen less psychotomimetic effects from THC than did the Lexington group.

Studies of Oral Doses of Marihuana Extracts: We have completed several experiments with extracts of marihuana, gauging doses on the basis of THC content. We used doses ranging from 5 to 60 milligrams, and compared these to each other and to the placebo extract. At the smaller doses, appreciable clinical effects were usually observed as compared with placebo; at the larger doses, psychotomimetic effects were observed. In general, one had the impression that the effects produced by these extracts were comparable to those which would have been produced by similar doses of synthetic THC.

Tests comparing the effects of doses of marihuana extract containing the equivalent of 20, 40, and 60 milligrams of THC with the effects of placebo indicated that whereas long-term memory (tested by subtraction of serial sevens) was maintained, short-term memory (tested by the span of forward and backward remembered digits) was impaired. Along with this was an impairment of a more complex task, goal-directed serial alternation, in which successive subtractions and additions had to be made to reach a specified end number. The latter task requires the retention, coordination, and serial ordering of memories relevant to a specific goal which must also be kept in mind. Disturbance of this type has been termed temporal disintegration. Both confusion and depersonalization are prominent clinical features of the intoxication from marihuana (*16*).

We also compared marihuana extracts with ethanol and dextroamphetamine in regard to their effects on mood and mental functions (*17*). Marihuana and ethanol were most alike in their effects; they caused decreased activity and had a tendency to impair performance on certain psychometric tests as well as performance on the simple reaction-time test. Marihuana was distinctly different from the other two drugs in regard to effect on time estimation and production, with subjective time being slowed.

A group at the University of Utah has also used marihuana extracts in clinical studies. They, too, have been impressed with the disruptive effects of marihuana on sequential thought, which suggests impairment of rapid decision-making and short-term memory. They have noted, as have others, a great variability in performance during marihuana intoxication, which may be related to the fact that subjects go "in-and-out," the effects seeming to come and go. A later study by this same group used doses of marihuana extract containing

0.3 milligrams of THC per pound (0.66 mg/kg) of body weight. Performance was impaired in complex reaction time, digit-code memory, time estimation, hand-steadiness, and reading comprehension. Once again, the sporadic nature of the experience was noted, with lapses in response while attention waned. Thus, impairment was explainable by loss of selective attention, immediate recall, and systematic thinking. They suggested that prolongation of time estimates might be a secondary phenomenon (*18*).

Studies with Smoked Marihuana: As marihuana is more commonly smoked than taken orally, some investigators feel that proper studies can be done only by utilizing this particular route of administration. The major argument is that smoking native marihuana may include other active materials present in the plant which are not found in synthetic THC or extracts, or that the process of combustion may create new active materials. No proof for either assertion is at hand. The disadvantages are great: the dose, even when one knows the amount in the cigarette, is impossible to judge as variations in technique of smoking may create tremendous variations in delivery of the dose.

The first such study provided marihuana in cigarettes, the putative doses being 4.5 and 18 milligrams, which were compared with a placebo smoke (*10*). Naive smokers experienced few subjective effects, although they showed an increased heart rate and reddening of the whites of the eyes. Experienced smokers of marihuana reported a typical "high," not much elaborated upon. Performance on the digit-symbol substitution test and the pursuit-rotor test was unchanged. No changes in blood sugar were found. In general, the effects of drug smoked in this fashion were relatively mild and innocuous, which led the investigators to take a sanguine view of the social use of the drug. It seems possible, in retrospect, that the doses in this study were far less than assumed, both on the basis of another investigator's experience with aged natural material (see below) and studies of synthetic THC.

Another study tested driving skill, with a driving simulator, in subjects 30 minutes after smoking two marihuana cigarettes over a 30-minute period and 1 hour after consumption of large doses of ethanol, as well as after no treatment. Under marihuana conditions, speedometer errors were increased, which suggests that the subjects did not monitor the speedometer as carefully as they might have normally, but driving was otherwise little impaired. As might have been expected, marked impairment was observed from the high doses of alcohol, which were intended to approximate concentrations of 100 milligrams per 100 milliliters of blood. Such highly controversial findings have elicited criticism because the doses of the two drugs were disproportionate, because a dose-response curve was not obtained, and because simulated driving might not be an adequate model for real life (*19*). Other objections are that smoking delivers an uncertain dose of drug and that most marihuana users tend to titrate their rate of smoking to a desired clinical "high," which in this case might have been lower than usual due to the subjects' bias in favor of marihuana over ethanol. The earlier study of smoked marihuana found that most effects dissipated by the end of 1 hour, so that the testing may have missed some impairment. Although the authors were careful not to state that the marihuana did not affect one's ability to drive a car, it is unfortunate that many lawyers and courts may draw this conclusion. Sometimes it is better not to be so scientific. Since our first experiments, we simply asked subjects when they were "high," "Do you think you could drive a car now?" Without exception the answer from those who had really gotten "high" has been "No!" or "You must be kidding!"

Ten experienced marihuana smokers who smoked two to three cigarettes containing a putative dose of 3.9 milligrams of THC each, had only minimum effects. Besides reporting a feeling of being "high," they showed a slight decrease in intellectual efficiency, some excess jocularity, and a slight loosening of associations. Neurological examination revealed a slight improvement in vibratory sense. The electroencephalogram showed slight slowing in the alpha band with more peaking of frequencies. Subsequent assays of the materials smoked in the above study revealed an almost tenfold decrease in its reported strength, emphasizing the difficulties in using the unextracted natural product, which seems to have a relatively short shelf-life. Ethanol extracts of marihuana, especially if kept cold and in the dark, maintain stability very well (*20*).

The electroencephalographic effects reported in the above study were similar to those we found following oral doses of marihuana extract that contained the equivalent of 32 milligrams of THC. However, the changes resembled those of drowsiness and were not readily distinguishable from those from the same subjects under placebo conditions, where some drowsiness also occurred (*21*). Others have reported somewhat different electroencephalographic effects, which reemphasizes the difficulty in corroborating such effects of various drugs.

Eight subjects smoked both placebo cigarettes and those containing marihuana extract in an amount equivalent to 10 milligrams of THC (*8*). Prior testing suggested that, even when smoked with maximum efficiency, only 50 percent of the dose in cigarettes was delivered, so the results were construed as representing an effective dose of 5 milligrams of THC. As compared with placebo, marihuana impaired performance on a pursuit meter, as well as on five of nine performance tests done under conditions of delayed auditory feedback. Subjects reported many more symptoms from marihuana than from placebo and were able to identify the active cigarettes without error; half the group thought the placebo cigarette was also active, once again confirming the unreliability of subjective identification, which may be biased by the procedure of smoking, the taste and smell of the smoke, and conditioning from past experience. A subsequent study by the same group, with similar doses of marihuana combined with a dose of ethanol calculated to produce concentrations of 50 milligrams per 100 milliliters of plasma, revealed evidence of an additive effect in regard to impaired functioning (*22*).

Ordinary cigarettes were dosed with marihuana extract equivalent to 12 milligrams of THC, placebo marihuana extract, Δ^3THC (15 milligrams), and synhexyl, a Δ^3THC homolog (15 milligrams) and were smoked in blind fashion by subjects habituated to nicotine. Even the placebo cigaretes produced an evanescent high, which testifies to the effect of the smoking process itself in contributing to some placebo responses. The cigarettes containing the active materials were clearly distinguishable on the basis of subjective effects, which resembled those well described for marihuana. Both Δ^3THC and synhexyl were somewhat less potent than THC in the extract, being from one-third to one-sixth as active (*23*).

Studies with Both Oral and Smoked Marihuana: Ten heavy users of marihuana smoked active marihuana and marihuana from which all active material had been removed (placebo), and

they ingested active and placebo extracts of marihuana and ethanol (*24*). Doses were the equivalent of 9 milligrams of THC for the active smokes, the equivalent of 90 milligrams of THC for active orally ingested material, and 0.95 grams of ethanol per kilogram. Not only did these subjects show little effect from the rather large acute dose of ethanol, but they were scarcely able to distinguish active smoked marihuana from the placebo. They uniformly distinguished the active oral dose, which was considerably stronger than the active smoke as measured by symptom reports. Both forms of marihuana increased pulse rate and time estimation; they had no effect on time production, the rod-and-frame test, and digit-symbol substitution. Ethanol had an opposite effect on time estimation, decreasing it. The electroencephalographic changes were described as increased low-voltage fast activity, decreased alpha activity, and slight slowing of the alpha frequencies. Because of the remarkable tolerance of these subjects to ethanol, as well as to a monumental dose of marihuana (if the putative oral dose was correct), the possibility of some cross-tolerance between alcohol and marihuana was raised.

Metabolism in Man: Until recently, very little was known regarding the fate of THC in man. We attempted to measure unchanged THC in plasma with gas-liquid chromatographic techniques without any success. Others with techniques of even greater sensitivity (detection of 600 picograms of THC) have also failed. A relatively simple technique for measuring the excretion of metabolites of marihuana in urine used thin-layer chromatographic techniques (*25*). The possible use of this test forensically is limited by the persistence of some of the new spots that appear after marihuana was smoked or ingested for periods far longer than the span of drug effect; we have found some present for 2 weeks after the last dose. With thin-layer techniques, we have not found measurable amounts of unchanged THC in urine, even when this was the sole substance given in very large amounts. Others have reported no cannabinoids as present in urine after marihuana smoking (*7*). Recently a 7-hydroxy metabolite of THC has been described, which also has pharmacological activity (*26*). Thus, it seems possible that the drug may exert its action through an active metabolite. The prolonged latent period following ingestion of synhexyl led us to propose that it must be converted to an active metabolite. On the other hand, conversion of THC to any active metabolite, if this is necessary for its action, must be swift, as effects of potent preparations are noticeable within minutes after smoking.

By use of tracer doses of THC (5.6 to 7.9 micrograms per kilogram) labeled with carbon-14, the disposition of an intravenous dose was determined in man. A two-phase biological half-life was found in the plasma, the rapid phase lasted about 30 minutes during which redistribution of the drug occurred and was followed by a slow phase of about 56 hours. As the rapid phase correlated reasonably well with the expected span of clinical effects of THC similarly administered, pharmacologically active doses of the drug might be handled in a similar fashion. Metabolites of THC appeared in plasma within 10 minutes, but during the first hour most THC in plasma was unchanged. The 7-hydroxy metabolite constituted only a relatively small fraction of material in plasma but other presently unidentified materials might represent further metabolites derived from it. Less than 1 percent of THC was excreted in urine unchanged (*27*). Intravenous injection of tritiated THC in rabbits revealed a shorter half-life, ranging from 7 to 16 minutes, with disappearance of most unchanged THC over a 30-minute period. In vitro studies showed that THC is bound to lipoproteins in human plasma to the extent of 80 to 95 percent. Thus, assumption of prolonged binding in tissues, as indicated by the prolonged half-life after redistribution of the drug, is quite reasonable (*28*).

Relevance of Laboratory Experiments to Social Use: One must always be concerned when one studies in the laboratory drugs that affect the mind lest the constraints of an experiment alter what one is measuring (the uncertainty principle in the behavioral sciences). Implicit in all research with these drugs are the influences due to the types of subjects, their expectations and past life experiences, the attitudes of the experimenters, and the setting in which the experiment takes place, all of which may alter the drug effects which are observed. Past experience with laboratory experiments involving psychotomimetic drugs indicates that such extraneous influences have been given undue emphasis. With proper information-gathering techniques, a basic group of clinical signs and symptoms can be delineated for various drugs that correlate well with those reported from their social use (*29*).

It is rather heartening, therefore, that the clinical syndromes described for marihuana in the laboratory correspond closely to those reported by street users (with the exception of those which are too personal or metaphysical to be measured). With a questionnaire technique and a sampling method that allowed distribution of the questionnaire until it reached a respondent who was a user of marihuana, clinical aspects of the social use of the drug were described (*30*). The most common symptoms and signs reported were: paresthesia, floating sensations, and depersonalization; weakness and relaxation; perceptual changes (visual, auditory, tactile); subjective slowing of time; flight of ideas, difficulty in thinking and loss of attention; loss of immediate memory; euphoria and silliness; sleepiness. Other common symptoms which are not verifiable in the laboratory were claims of increased insight and perception, as well as increased sexual desire, performance, and enjoyment.

On the basis of these data, one would assume that at least the respondents to this questionnaire had explored most of the range of marihuana dosage that has been studied in the laboratory. The resemblance of many of the effects reported to those previously reported from hallucinogenic drugs suggests that some of the doses of marihuana which are used socially are fairly high. In any case, laboratory experiments can be contrived which are highly relevant to the effects of these drugs as they are used socially.

Part of the problem in relating social use of marihuana to laboratory studies may be due to the fact that adulterated drug may be encountered in social use. Adulterants have included oregano, *Stramonium* leaves, methamphetamine, cocaine, LSD, and, allegedly, heroin, although use of the latter scarcely makes economic sense. Atypical reactions from marihuana use, at least those which seem to be unexplainable by laboratory studies of its pharmacological effects, might be better explained by the presence of a different drug.

Marihuana in Man: Future

Social Use of Marihuana: Much has already been written about the problem of the rapid spread of marihuana usage, especially among younger Americans and Western Europeans (*31*). Unfortu-

nately, we lack many important facts for making a proper judgment about the desirability or undesirability of accepting this drug into our culture. Here are some important, but not fully answered, questions. Most of these are not answerable by laboratory experiments.

Is marihuana to be equated with alcohol as a social drug? This assertion is often made by its proponents, who view it as a desirable substitute. In terms of its extraordinary low acute toxicity, as compared with alcohol, marihuana would appear preferable. The fact that it is noncaloric is another advantage, as many medical complications of alcohol stem from the fact that it is an inadequate food. On the other hand, the degree of impairment from casual or continued use seems to be about equal for either drug, assuming that equivalent mind-altering doses are taken. One of the great present difficulties is that the dose of marihuana is exceedingly difficult to gauge in its presently available forms, whereas that of alcoholic beverages is most precise. This disadvantage might be overcome in part by synthetic THC's, which afford a rather precise, but not nearly so palatable, method of titrating dose. Unlike alcohol, which is almost totally absorbed, oral doses of THC are absorbed to a far lesser extent. Delivery of a dose of drug by smoking is even more uncertain. The greatest problem is the assumption that marihuana would supplant alcoholic beverages for a great number of people. Past history suggests that the drug would simply be added to the use of alcoholic beverages by many, or even be used by sizable numbers of people who ordinarily might not take social drugs at all.

Another aspect of the comparison between marihuana and alcoholic beverages has to do with the ostensible reasons for using them. Few people admit to taking a drink to get "stoned" (in the old days this term was applied to the effects of overdoses of alcohol), but rather because they enjoy the various highly palatable forms in which beverage alcohol is available or the various social occasions at which its use is socially sanctioned. Marihuana, on the other hand, can be used only for the drug effects. The smoke is hardly enjoyable in its own right, much less the rigorous method of smoking, and the noxious taste of orally administered forms of the drug is virtually impossible to disguise. Whatever esthetic benefits marihuana may provide must be attributed to the drug effect and not to the process of taking the drug. Thus, in considering the social use of marihuana one must justify drug-taking in its own right without the various social conventions surrounding the use of alcohol, nicotine, or caffeine, as these drugs are presently used socially.

How serious is the dependence problem with marihuana? Psychological dependence has been well documented, but physical dependence manifested by withdrawal reactions is unknown. To this extent, one might assume that marihuana might be easier to give up than are alcohol or sedatives. Nonetheless, where the drug is freely available despite legal restraints (such as in Egypt, not to mention the United States), many people use it repetitively. A study of such users in Egypt revealed that the amount of use varied from 5 to 50 times monthly, that most users started before the age of 20 years, and that the principal reasons for starting were to be socially conforming, to satisfy curiosity, and to attain euphoria and sexual stimulation. Although two-thirds of the users expressed a wish to discontinue, their habituation to the euphoriant and soothing effects, as well as their continuing need to conform to a now-expected social pattern, made them continue use of the drug (*32*). A similar pattern seems to be emerging in the United States.

Does marihuana use lead to opiate addiction? This point is highly controversial, and it may be too early to provide an adequate answer. In many parts of the United States, especially the northern urban centers, opiate addiction is related to prior use of marihuana (*33*). Yet, it is also apparent that only a small number of all marihuana users follow such a progression. If anything is clear, it is that the availability of a drug is directly related to its nonmedical use and that such use of any drug increases the likelihood of multiple drug use. As the phenomenon of widespread use of marihuana by youth in our country is still comparatively recent, it remains to be seen whether the number of persons in their early 20's who are dependent upon narcotics will increase during the early 1970's, when such a phenomenon might be expected to occur if there is progression from marihuana to more potent agents. During the past 2 years, it appears that multiple drug use among our youth has led many to become heroin addicts. The present pattern of heroin use by white, middle-class, native-born, suburban youth contrasts sharply with the pattern of use by poor, culturally unassimilated, central city residents which had been stable for the previous 25 years.

What are the immediate and remote dangers of marihuana use? As more reports come in, it appears that the immediate dangers are almost identical with those from LSD, probably because at higher doses many of the same mental and emotional reactions are obtained. Manic or elated excitement, panic states, precipitation of schizophrenic-like or depressive illnesses, and frank deliriums are infrequent complications encountered among users (*34*). What is more disturbing are reports of subtle effects on the personality associated with prolonged use—loss of a desire to work, loss of motivation, and loss of judgment and intellectual functions (*35*). It may well be argued that individuals with these manifestations may have developed them in the absence of drug use, but available evidence does not allow this assertion. In view of the fact that many drug users are recruited from segments of our youth most favored with intelligence and opportunity, the future loss of a large number of these individuals from productive society could be of considerable social consequence.

Should marihuana use be legalized? Again the example of alcohol is cited. This seductive solution would have several immediate benefits: it would reduce the number of possible crimes one can commit, it would provide a legal source of pleasure, it would provide another source of taxation, and it might serve to reduce tensions between races and generations. Arguments for legalization of marihuana have been extensively set forth and are superficially quite convincing (*36*). A distinction should be made between legalization and making something "less illegal" as by eliminating penalties for possession for personal use. Legalization of marihuana would require the government to take over the licensing and control of the production, manufacture, distribution, and sale of marihuana products. The same enormous bureaucracy which is required to control alcoholic beverages would have to be duplicated or expanded. Control of marihuana might be far more difficult to achieve than control of alcoholic beverages. No one feels constrained to watch over every field of corn, but would anyone dare leave a field of marihuana unguarded? And no one can produce a potable alcoholic beverage easily from that corn, but the weed comes ready to use. Bootlegging of beer and

wine is possible, but not especially easy; anyone with a window box can bootleg marihuana. What legalization might very well produce is the same type of disrespect for the law deplored by those who object to the present marihuana laws. Increasingly it is becoming apparent that the criminal law is not a suitable means to control the problem of drug abuse; it has failed in virtually every instance (*37*). What may be more immediately appropriate would be to eliminate penalties for possession of marihuana for personal use, not to establish a new body of law that might prove to be as difficult to enforce as the one we have. Other countries are coming to similar conclusions about the amelioration of marihuana laws (*38*).

Pharmacological Questions: Undoubtedly, the next few years will see a rapid expansion of our pharmacological knowledge about marihuana. Many talented people have entered the field, for a variety of reasons. It is unlikely that pharmacological answers will provide answers to the social questions about the drug. In this instance, as in all others regarding nonmedical drug use, the problem has many dimensions.

The true potency of THC has not been fully explored as yet. As techniques for administering the material by inhalation improve, it seems to be more potent than originally believed. Very likely an acceptable form for intravenous use, binding drug to species-specific albumin, will soon be available. Even now, the potency of THC, either as a hypnotic or as a hallucinogen, is substantial in comparison to other drugs. Whether or not THC is the major active material in marihuana should become clearer soon, as it becomes possible to test separately other cannabinoids for pharmacological effects. Although there seems to be no question that Δ^6THC is also an active material, it constitutes such a small fraction of cannabinoids in the natural plant that its contribution must be negligible. Alkaloids may be found in the plant, but it remains to be seen whether these are pharmacologically active or present in significant quantity. Finally, the possibility exists that other materials in the plant, even though inactive in themselves, may interact with THC to make it more active, or may be converted to active materials within the body. These questions should be settled equally well by tests of the materials given orally as well as by smoking; to date there is little evidence that pyrolysis creates any new or greater amount of active materials than was originally present in the plant.

If THC should prove to be the major active natural constituent, it may still not be the active material in man or animals. Active metabolites have been described for both THC isomers, representing hydroxy-derivatives of the free methyl group (*26*). It is still uncertain that these metabolites constitute an important product of the metabolism of the drug in man.

To date, not much study of various THC isomers and homologs has been accomplished in man. Both THC and Δ^3THC are active when smoked, but the latter is far weaker; it has about the same potency as synhexyl, a Δ^3THC homolog with a somewhat longer side chain (*23*). Other isomers are possible, but have not been explored, although it is likely that Δ^6THC will soon be tested in man. Side chain variants may selectively single out specific types of pharmacological effects; the dimethylheptyl side chain configuration has the strongest hypotensive effects. Homologs containing nitrogen have also been prepared and have shown pharmacological activity in animals. Consequently, we may expect to see an increasing number of marihuana analogs and homologs developed during the next several years. Relationships of structure to activity should become clearer as these are studied in man.

The questions of tolerance, or possibly "reverse" tolerance, is of some interest. The only study of chronic dosage of marihuana, as well as synhexyl, in man indicated that tolerance in the usual sense occurred (*39*). It was not of great degree and no definite withdrawal symptoms were encountered. Recent work indicates that tolerance can be produced in two animal species (*40*). On the other hand, pharmacokinetic considerations would lead one to believe that any drug with such a prolonged secondary biological half-life (56 hours) as THC should show increasing effects with repeated doses, or so-called reverse tolerance. This will depend upon whether or not the secondary biological half-life really applies to THC or other active materials, rather than inactive metabolites. The notion of reverse tolerance undoubtedly includes some learned effects about the proper method of smoking and what symptoms may be anticipated, as well as the placebo effect which chronic use of marihuana seems to develop. Perhaps this learned sensitization minimizes true pharmacological tolerance of mild degree, so that chronic users do not feel constrained to increase their dose to maintain desired effects.

Interactions between marihuana and other drugs used socially will undoubtedly be studied soon. Among the lore of the street, it is a common practice to drink sweet, fortified wines while smoking marihuana to enhance its effects. From what we know of the effects of these two drugs, they have much in common, so the practice seems to be well based. One might expect some degree of additive effects with barbiturates, but a more complex, mixed pattern with amphetamines and hallucinogens. Curiously, such combinations, other than that mentioned for alcohol, are seldom used socially.

Elucidating the mechanism of action of drugs is the holy grail of pharmacologists, but it is seldom achieved. In view of the current emphasis on the action of psychoactive drugs on brain biogenic amines, one might expect a great deal of work on this area. Preliminary studies have been rather ambiguous, due in part to the difficulty in administering doses of drugs to animals, as well as experimental constraints in man (*41*). Some of these difficulties should be overcome, and with increased supplies of drug, an abundance of studies of the mechanism of action will soon ensue.

Therapeutic Potential: One of the most prominent pharmacological effects of marihuana or THC is its sedative-hypnotic action. As such drugs are extremely popular, it is likely that some attempts may be made to exploit this effect therapeutically. Several difficulties seem evident. First, the onset of the action of oral doses of THC is often rather slow, contrary to that of conventional sedative-hypnotics. When the drug is smoked, the onset is rapid, but the duration is relatively short. Thus, it seems impossible with current methods of administration to attain both a rapid onset and long duration of action. Second, doses high enough to produce a marked hypnotic effect are almost always accompanied by some degree of psychotomimetic-like perceptual disorders, which many patients might find disagreeable. Third, the fine titration of dose required to provide sedative effects is likely to be difficult. Finally, the drug does not have novel effects compared with other sedative-hypnotics. Because of the frequent report of dreamlike states during marihuana intoxication, we tested its effect in the sleep laboratory. The effect on rapid eye movement sleep was similar to that of more conventional hypnotics, in that a mild dose caused a tendency to decrease time spent in rapid eye movement sleep (*42*).

Analgesic effects from *Cannabis* have been described for a long time. They are also demonstrable in animal screening tests, such as the rat tail-flick test. Whether such analgesic effects are secondary to the hypnotic effects, or more similar to those of opiates, is still unsettled. In any case, the place of opiates or opioids for treating severe pain or even that of codeine for treating milder pain will be difficult to challenge, either in terms of rapidity of onset, duration of action, or presence of tolerable side effects.

Despite some superficial similarity of the effects of marihuana to those of barbiturates or opiates, it is likely that this drug is not a pharmacological equivalent of either of the latter. Thus, it would seem to be an unlikely candidate for treating withdrawal reactions to alcohol, barbiturates, or opiates. Clinical trials for this purpose were undertaken a number of years ago, but despite some initially favorable reports, this use did not catch on (*6*, *43*). In view of the present abundance of drugs which are satisfactory for treating withdrawal reactions, marihuana is not likely to offer any compelling advantages.

The sedative and euphoriant effects of marihuana might seem valuable for treating depression, where anxiety and sadness are often the rule. Past attempts to treat depression with marihuana did not attract much interest, but it could be that the times were prejudicial to its wider use (*44*). As sedative drugs may be of value in treating common types of depression mixed with anxiety, marihuana could be useful, but probably no more so than the conventional sedatives so widely available. The actions of tricyclic antidepressants, which are clearly the drugs of choice for endogenous or retarded depressions, are quite different from marihuana, which would not supplant these agents in these more severe depressive syndromes.

Street lore has long had it that one's appetite becomes ravenous and one's appreciation of food sublime after use of marihuana. A recent attempt to study this appetite-stimulating effect in the laboratory gives some support to this idea, although it is by no means a constant phenomenon (*45*). As it has not been studied in patients whose appetite is poor, but only in subjects with normal appetite, one cannot draw conclusions about its clinical utility. Further, to be truly useful in the clinic, this effect would have to be sustained over time.

The hypotensive effects, both of THC and especially of homologs such as the dimethylheptyl derivative, have engendered hopes that some derivative might be a useful therapeutic agent for essential hypertension. Hypotensive effects have only been attainable with doses of THC which have severe mental effects. Although the mechanism of its hypotensive action has not been worked out, it may be due to blocking of compensatory mechanisms for maintaining blood pressure in the erect posture. As this mode of action is perhaps the least desirable mechanism for lowering blood pressure of the several available, and many other available drugs work in this way, the possible therapeutic use of some THC derivative as an antihypertensive drug is doubtful.

Other uses which have been proposed for marihuana include the treatment of epilepsy, as prophylaxis for attacks of migraine or facial neuralgia, or as a sexual stimulant. These are more speculative in nature, but because suitable drugs are lacking for at least the last two uses, they will probably bear some investigation.

Summary

The past 3 years of renewed research on the effects of marihuana in man has added little not previously known about the clinical syndromes produced by the drug. The major advance has been a quantification of dose in relation to clinical phenomena, and a beginning of an understanding of the drug's metabolism. The crucial clinical experiments in regard to the social questions about marihuana, such as the possible deleterious effects from chronic use, cannot be answered by laboratory experiments. These must be settled by close observations made on those who experiment on themselves. It should be possible, within a relatively short time, to determine whether marihuana has any medical utility, but the future would appear to be no more promising than the past in this regard. The mechanisms by which marihuana alters mental functions are not likely to be answered in man, nor even answered soon by animal studies. As marihuana may be unique among drugs in that more experimentation has been accomplished in man than in animals, it may be necessary to look to additional animal studies to provide leads for pertinent future studies in man.

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Mission-Oriented R & D

Senator Mansfield's questions sharpen congressional uncertainties about federal R & D patterns.

Rodney W. Nichols

Congress has a wonderful knack for asking fundamental questions about public policy. Recent questions about "national science policy"—implying that such a policy is extinct or embryonic, indispensable or impossible—reveal the fact that many congressmen think they have not been getting fundamental answers.

Answers have been based upon a rhetoric that has enlivened and served the R & D (*1*) community since World War II. Basically, it describes a logical framework of national goals and agency missions, not national science. Now the rhetoric seems fatigued. It may still be valid, but it certainly is not persuading Congress to support basic research. Many members of Congress don't believe it at all.

There still exist the same institutional patterns for R & D that once seemed to represent the best interests of government, industry, and universities. Indeed, they seemed to serve the goals and missions of the people. These patterns are now challenged; they are, perhaps, crumbling. They may be worth preserving, but Congress isn't sure they are—neither are some members of the R & D community. If new patterns for R & D in the United States are drawn, will the great public goals be served as well in the future as some think they were in the past? In fact, given the rising and varied demands of the day and the declining enthusiasm for R & D, will some goals be reached at all?

Three factors that bear on the future of mission-oriented R & D are discussed here. The first is one of Congress's most famous recent actions affecting mission-oriented R & D: the "Mansfield Amendment," which attempts to curtail the non-mission-oriented research said to be supported by DOD. The Mansfield Amendment is important not because its direct effects have been great, but because it is the formal expression of deeper congressional concerns, the tip of an apparently large iceberg—and it does have the stamp of the Majority Leader of the Senate.

The second factor is the almost bewildering array of countervailing forces, in Congress and elsewhere, that have shaped the environment in which the Mansfield Amendment was passed and that have undermined the old rhetoric about federal support of R & D. The third consists of recent budgetary trends and some speculations about future trends in federal support for R & D. I have also presented a few of my own judgments on what ought to be done by the federal government and by the R & D community.

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Section 203—Beginnings

Section 203 of Public Law 91-121, the military procurement authorization for 1970, specifies that: "None of the funds authorized to be appropriated by this act may be used to carry out any research project or study unless such project or study has a direct and apparent relationship to a specific military function or operation." On 11 August 1969, Senator J. William Fulbright proposed the provision on the floor of the Senate as part of a broader amendment that cut funds to be authorized for Defense R & D. The amendment was passed on 12 August after desultory debate, without a word being said about Section 203. After the vote, Senator Mike Mansfield, taking the floor to praise Fulbright's amendment, said he had prepared an amendment identical to Section 203. The Mansfield Amendment, therefore, should have been attributed to Fulbright. But the popular name may be best, since Mansfield has relentlessly questioned DOD—as well as other federal agencies, including the White House science staff—about the implications of implementing Section 203. For example, in a letter of 22 September to John S. Foster, Jr., director of Defense Research and Engineering, Mansfield said he was concerned "with the vast expenditures of the Department of Defense for research and development" (*2*). He warned that "we must seriously inquire about the future role of the Defense Department in funding university research."

On 20 November 1969, the day after Section 203 became law, Mansfield wrote to Secretary of Defense Melvin Laird, saying that the "specific intent