CONCLUDING REMARKS

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It is significant that this meeting was sponsored jointly by two divisions of The New York Academy of Sciences—Biology and Psychology. This is a unique situation and is indicative of the solvent power of these new drugs in bringing together the body and the mind.

In his introduction, Beckman urged that we pay attention to the etiotropic action, as he well called it, in contradistinction to the action of agents on symptoms. It has also been said that tranquilizers (or ataractic drugs, whichever term will eventually be accepted) make it possible for us to change disturbed mental patients into undisturbed mental patients. Actually, after much discussion we are not even certain whether meprobamate should be regarded as a drug of special interest in relation to mental patients or in a quite different light. This brings me to the first of the four topics I should like to consider: (1) classification, (2) the mechanism of drug action, (3) the problems of testing, and (4) the control of the tension level.

Classification

Classification has been much discussed within these pages and is actually very important in one's orientation; it is not a matter of purely academic interest. As was pointed out by Smith, patients given a drug that has become associated with the treatment of mental disease accept it unhappily, even though they are being treated for some totally unrelated illness. Also, the intellectual context of the agent matters a good deal to the physician. If meprobamate is like aspirin, it can be compared with a certain group of drugs; if it is like chlorpromazine, it is another matter, and it should be compared with a different group of drugs; if it is like mephenesin or zoxazolamine, the situation again is quite different. Greenberg has compared meprobamate in the alcoholic-ward units with morphine and with the barbiturates. Smith has compared it with other muscle relaxants, as has Schlesinger. Reserpine has been compared with one group of agents by one investigator concerned with blood pressure and with another group by another investigator concerned with mental disease. The classification makes a great difference in what one is likely to do or to see, and in the kind of answer obtained.

I remind you of the two priests, addicted to cigars, who were very unhappy over having been prohibited to smoke while participating in the long hours of prayer demanded of them. The two men decided finally that it would do no harm for each to write his bishop and ask for a relaxation of this proscription. One received the answer "no"; the other, the answer "yes." The first had asked, "Is it permissible to smoke while praying?"; the second, "Is it permissible to pray while smoking?"

I do not know what eventual decision will be made as regards the use of these particular drugs, but it will surely be of importance. I suspect that if a given drug finally turns out to be particularly useful in the treatment of psychoses and, therefore, receives the label "tranquilizer," it may help one

million individuals, at most. If the drug turns out to be more valuable in the treatment of neuroses and is given the label "sedative," it may prove useful in six million cases or more. If it turns out that the drug is such a minor agent that it will help only to put people to sleep and is labeled "hypnotic," then it will be used by perhaps twenty million or more people in the United States alone.

Regardless of the practical importance of classification, however, it will do no good to force the issue prematurely. The right terms, in fact the mere existence of terms, must follow the initial development of language, and then of science. I suggest that the words we now use in and out of our professional activities have come into being because, first, someone has noticed a phenomenon in nature; second, he has become sufficiently interested in it to identify it as distinguished from other phenomena and to describe it thus publicly; and, third, he and other persons now interested have communicated to one another their discoveries concerning it with progressively increasing descriptive power. In order to communicate effectively a greater perceptual awareness and discrimination, more and more differentiating words are needed. As is well known, the Eskimos have eighty words describing different states of solid water, while we have only six or eight. Snow and ice have more importance in the Arctic than they have in warmer regions.

So far I have considered the development of language for the discriminative identification of subclasses as one step, but this by itself does not lead to a scientific understanding of the situation. The rudiments of understanding appear when the next step is taken, when some attempt is made to classify or to analyze these different subentities—to put them, at least, into some kind of taxonomic scheme, hopefully, into one that fosters further understanding. As an example of the difference between the two steps, advertisers have taught us a great array of names for different colors. Names are chosen, presumably by practical application of the science of psychology, that will have the greatest possible appeal to women in order to induce the purchase of particular objects. When the wave lengths of any particular color have been established, however, the descriptive term becomes meaningless; as soon as the notion of a spectrum and ordered wave lengths comes into being, the whole collection of terms for color can be replaced by a precise and significant spectral notation. Obviously, therefore, it becomes of the greatest importance to analyze the mechanism of action of these drugs rather than simply to describe their over-all effects.

The Mechanism of Drug Action

I confess to having been astounded at the statement of one clinical participant that the tension that prevents sleep is abolished by the action of meprobamate on the hypothalamus. I was surprised that anyone had found this out so precisely and was able to make a positive statement about it. I was even a little surprised at the more cautious clinician who, in effect, apologized for not being able to answer a question regarding the site of action of meprobamate on the nervous system.

Leo Alexander has made a point worth considering in offering a complex method of distinguishing between anxiety located in the hypothalamus and depression located mainly in the cortex. With this attempt I found myself

in sympathy, as I have made similar efforts in the past and, especially, as Alexander has claimed that his method permits realistic testing. I should even like to suggest the kind of test that would serve in this case. At least one critical action of the mechanism that he described as at work was a negative feedback from the upper to the lower level. Too much anxiety in the lower level fires the upper level, which then inhibits the lower level, so that anxiety tends to be relieved by excess depression. This would mean—if one takes the dangerous liberty of equating mental phenomena with neurophysiological mechanisms—that, where this happens psychologically, appropriate parts of the hypothalamus are being inhibited. In turn, this means that the threshold to a stimulus should be raised there. An indwelling electrode in an appropriate hypothalamic region should then reveal a rise in electrical threshold at the time of depression or anxiety. I say this, of course, in partial jest, but if one does pretend to test hypotheses of this sort objectively, this is how it must be done and, at least in using animals, it is perfectly possible to do so. In fact, my associates and I did just this in studying the action of epinephrine on the central nervous system. Probe electrodes in different regions determined threshold changes—of motor cortex, knee jerk, and hypothalamus—after the administration of various doses of epinephrine.

Nevertheless, this positive statement serves to point out the present negative situation. Even such a serious attempt to find a method that will formalize drug action and lend itself to objective testing on humans is, today, more or less a dream. However desirable such an attempt may be and however fruitful it may ultimately become in accounting for the action of these various agents in terms of their precise mechanisms of influencing the nervous system, at present it would be premature to make any dogmatic statements regarding mechanism. I doubt if anybody knows enough about any drug to have more than a private opinion as to the directions and significance of his laboratory explorations.

Let me exemplify with one "fact," accepted for many years and referred to many times throughout this publication, that seems to me an illegitimate extrapolation from the actual experimental data. I refer to the statement that mephenesin acts by inhibiting interneurons. As far as I know, mephenesin depresses the polysynaptic more than the monosynpatic reflexes. It is possible that it does so by interfering with interneurons; but it is a gross extrapolation of existing knowledge to accept this as a fact in the absence of other evidence. Almost any nonspecific deleterious influence on the spinal cord—low oxygen, low temperature, low sugar, wearing out of the preparation—is likely also to depress the multisynaptic more than the monosynaptic reflexes, and would do so even if all cells and synapses were affected alike. The reflex that requires the most facilitation at some junction would be the first to fail; the more synapses, the more likelihood of this effect. There may be no quantitative difference at all between cells. Many types of neurons do exist in the cord as well as in the brain, and specific drug actions are quite reasonable. I doubt, however, that such an effect has been demonstrated here.

I choose this point, not to denigrate our presumed knowledge, but to emphasize, in a case where even the laboratory scientist has dared to make positive

statements, how careful one must be in drawing such conclusions. In fact, it is precarious even to state that a drug is a stimulant or depressant to the nervous system when the observation is based on a change in total behavior and sometimes even when it is supported by particular observation of the activity—for example, the electrical responses—of one center or another. Recall the simple balance, with a pan on each end and the pointer centered at equality. An increased weight on one side, adding excitation, or a decreased weight on the other, removing inhibition, would tip the pointer to overactivity or "excitation," and the reverse to underactivity or "depression" of total behavior. A drug that stimulates all neurons can add weights on both sides, can tip the scales to convulsions or to coma, depending on whether the action is greater on the excitatory or the inhibitory systems. A drug that is a general depressant can do the same. Without real knowledge of the actual situation, any conclusion as to mechanism is dangerous.

It is even useful to raise the question whether a given drug at different doses always has the same action in varying degree, or can reverse its action, or can act in different ways in different places. At the most general level there is a quantitative gradient along the neuraxis; the upper end is most active metabolically and physiologically—as the pacemaker of the heart is—and the more active regions are knocked out by progressive depression more easily than are the less active areas. Thus anesthetics knock out the "higher" centers before the "vital" centers of the brainstem and so permit anesthesia without death. Hypoglycemia, or low oxygen, also gives a progressive chopping off along the quantitative gradient. On this basis one might think of some drugs as producing effects at the upper end of the nervous system more easily than at the lower end. Relatively speaking, such drugs presumably would modulate the finer nuances of behavior and subjective experience more than they would depress or exaggerate the reflex behavior of the lower part of the nervous system. However, it is equally possible—in fact, it is one of the great hopes of psychopharmacology—that specific chemical agents may differentially activate, depress, or modify the behavior of particular functional systems in the nervous system. If this proves to be the case, such drugs will make fine tools—in contrast to such gross tools of regional lesions or stimulation—for working out the concomitant variations in personality, in symptom complexes, and in clinical entities, and for relating them, ultimately, to particular detailed functional subsystems of the nervous system.

The paper by Baird *et al.*, showing a differential action of the drugs concerned here on various parts of the basal nuclei, is relevant to this point. Quite aside from action at a general level, and without specifically affecting particular parts of the nervous system, a drug may have profound effects simply by altering time relations. This may be the main moral of Hess's paper on imprinting, in which the exciting observation was made that, with drugs, one could delay imprinting—the nervous system of treated ducklings did not imprint at the age of 13 hours, as it normally does, even though the ducklings were wobbling about, but at 20 hours or at some subsequent time. This implies a change in tempo of the maturation process itself. Further, it was suggested that this particular imprinting was merely one stage in the development of the nervous system, that there are specific times for imprinting such characteristics as

docility, mating behavior, decent performance in the herd or, more broadly, socialization, and the like. I wonder if there exist specific kinds of susceptibilities of the nervous system at different times or if the cumulative behavioral capacities allow the fixation of more and more complex patterns.

Let me generalize still further. The whole of biological and psychological development is a series of appropriate reactions to appropriate experiences in the right sequence. Drugs that would simply slow up certain activities or throw them out of phase with others could have tremendous impact on the behavior, even though no particular cell were stimulated or depressed and no particular enzyme were rendered ineffectual or activated. It could all be a disturbance of the patterns rather than the units. This deserves emphasis. If, from a paragraph or even a sentence of type, we drop out all the e's or all the t's, we should probably still be able to read the text without difficulty. Dropping out such a series of letters would be equivalent to knocking out a major enzyme system. If, however, we leave all the letters in any passage, but mix them up, there will be practically no chance of our making any sense of it.

Returning to the problem of gross levels, it has been said that a battery of careful psychological tests given to patients of various kinds has indicated that dexedrine had the same effect as that of a prefrontal leukotomy; chlorpromazine, as that of a cingulate gyrus lesion. I do not know whether these findings will hold up, but this seems to be a useful kind of approach. This is the way, more precisely, to establish a link between the anatomical and physiological on the one side, and the behavioral on the other. At the Mental Health Research Institute last year we tried a similar experiment. Individuals were made hyperthyroid and were returned to normal in the hope that responses to a certain group of psychological tests would change, but that others measuring different parameters of the psyche would not do so. Unfortunately, the results did not show a clear separation.

I should like to consider specifically the question of muscle tone and steadiness, and tremor and anxiety—they do link up physiologically—because they have received so much attention. I remind you that the degree of alertness of an individual, whether awake or asleep, is determined by, among other factors, the degree of muscle tension, and so by the feedback from the muscle proprioceptors and the flow of impulses up to the higher centers. Various agents cause both increased tension and tremor and increased anxiety. One of the best examples is epinephrine itself, which is liberated in association with anxiety and thus can serve as a positive feedback mechanism. Dickel reported, however, that his patients, given meprobamate, showed a substantial decrease in the action potentials of their muscles, but no change in the psychological concomitant of anxiety and worry. Harriet Gillette attempted to analyze the drug action neurophysiologically and to distinguish between pyramidal and extrapyramidal defects—certainly a step in the right direction. She also made inferences that conformed with those of Schlesinger, but with a somewhat less positive final conclusion as to their present usefulness.

I conclude by saying that, although I completely favor experimental analysis of the action of these drugs and regard this as ultimately the necessary and sound way of ascertaining their potentialities, and so of improving the drugs

and their actions, I think we must be very careful not to reach premature and uncertain conclusions. For the time being, those who hold to a statement of what they actually observe—the flaccid feel of a muscle, the occurrence of certain electrical changes, the particular performance of a patient—are likely to contribute most.

I am especially directed toward this conclusion by the exchange between Berger and Pfeiffer, the two pharmacologists who have actually tested meprobamate in some detail on animals. These investigators could not even agree on the actual experimental findings in a number of instances. Obviously a third element will be needed to resolve this. Since one of the disagreements involved the question as to whether patients under meprobamate slept quietly or squirmed around in bed like eels, I could not help but remember the story of the electrophysiologist who led an expedition up the Nile and brought back an electric eel to study. The eel gave shocks nicely for a while, but then grew despondent, slumped in the aquarium, and would not perform. The experimenter had learned something of the eel language and when he asked why, the eel replied, "It is the mating season now, and I am lonesome. I should like another eel." The experimenter, being human as well as scientific, arranged another expedition, and soon a female eel was put in the tank. After a moment of twining ecstasy, however, the two went to opposite sides and the first eel was more despondent than ever. When asked again, "What is wrong? " he said, "Alas, I am A.C. and she is D.C.!"

The Problems of Testing

I shall deal briefly with the problems of testing, since they have been discussed at some length in the recent symposium "The Evaluation of Pharmacotherapy in Mental Illness." Questions raised in this publication that were extensively discussed in that conference include: behavioral toxicity, which does need much emphasis in dealing with behavior-affecting drugs, agents that yield the particular effect desired only at some price, in performance if not in liver function; the problem of transferring to man the results of experiments made on animals; and the influence of a group of patients on the effects of a drug—raised here by Sabshin, Greenberg, and others.

I was impressed by the report of the different relative effects of the drugs on different nursing units. Partly, this seemed related to the severity of the disease, but partly it seemed related also to the unique personalities or individualities of the units. When Greenberg pointed out that, in the alcoholic institute, even placebos gave almost 40 per cent improvement (meprobamate gave twice as much, and the difference was significant statistically) I wondered whether the subjects had been located in the same units. The progressive quieting of the unit, due to the actual soothing of disturbed and disturbing patients by the drug (and obviously easily measurable by a global index, such as the decibels of general noise level of a ward), might have decreased the tensions of those not getting meprobamate, so what was regarded in this case as a placebo effect may have been, so to speak, a reverberation of quiet from the true action of the drug. Similarly, one's own level of conversation fluctuates, depending upon the noise in the room. The installation of soundproofing in a ceiling by itself can lower stress.

At the experimental level of drug testing, the particular problem is that of determining the proper factor for which to look. There is no sense in trying an agent on an animal or on a human who does not manifest the phenomenon the agent is expected to influence. It would have been difficult to find the antibiotic activity of penicillin by giving it only to healthy animals and men. Thus, either the kind of symptom to be influenced must be clearly present or it must be produced. Producing symptoms (convulsions, hallucinations, anxiety) with one drug and then searching for the drugs that will counteract these symptoms is similar to the case of the eminent neurologist who was approached by a patient for treatment of her indigestion. He assured her that he did not treat indigestion, but she insisted that he had been very highly recommended and she wanted him as her doctor. After a long argument he finally said, "I can give you a medicine that produces fits, and I am expert at curing fits."

Next comes the problem of the validation of findings and the relation to dose. On certain phenomena drug action was obtained only at very high doses. This seemed the main import of Hunt's experiments with meprobamate, and equally of Pfeiffer's. On the one hand, laboratory studies indicate that meprobamate is quite inert; on the other hand, a great number of takers seem to experience some benefit, and clinical reports included in these pages—many seemingly well controlled and convincing enough as reported—indicate a definite action. From this one must conclude either that the experimenters have not yet found the right thing to test—which would not be surprising, since we are dealing with agents active on the nuances of complex human behavior for which it is difficult to find electrical or chemical indicators, either in the laboratory or in the patient—or else that the clinical impressions are wrong and that some day these will follow phlebotomy, laudable pus, and other major medical mistakes into the discard. I doubt that the latter is the case, especially because of the genuine awareness of the problem of controls that exists today among the better clinicians and laboratory workers handling these problems.

We have heard much about the double blind and the placebo. The double blind has been described as an experiment in which everybody but the doctor knows what is being given; a report of a double-blind experiment on promazine and chlorpromazine, which act very similarly, supports this definition. The statement was made that the patients knew by the end of the first day whether they were getting *A* or *B*; that the ward attendants and the nurses knew which were which by the end of the second day. Greenberg has stated that, as regards meprobamate and placebo, the case was reversed; doctors, either more intelligent or having more contact with the patients, became aware of the results before the ward attendants did (I do not know whether or not the patients ever did).

A placebo, of course, means something that placates or pacifies or tranquilizes —perhaps we should really use the word "tranquilizer" for the placebos and not for the drugs being tested—but from evidence presented in these pages, they seem to have had a dynamic and exciting influence rather than a pacifying one. In general there has been a tendency to regard placebos in an "all-or-none" fashion and to take hostile positions concerning them. Some statements have been made that I should not have made myself. For example, it is well to compare the unknown agent, not with a completely inactive substance, but

with another agent possessing comparable activity. Here the observer is, so to speak, titrating a smaller difference, and this can be magnified more. Again, the need for using a placebo of any kind depends on the particular situation involved. With a sufficiently objective measure of something not immediately responsive to suggestion (either in the patient or the doctor), it is patently unnecessary to use a placebo. This resembles the situation in the chemical laboratory, where the agent is added to one test tube and not to the other; it is not necessary to add a like amount of water to a third tube just to fool it. Consider the case, described by Schlesinger, of certain patients who, after showing negative results for years on being tested with one after another agent, suddenly responded positively to a new agent. One could be pretty sure, in this case, without using a placebo and barring other significant change, that this agent was active.

The clinical "hunch" must always be the first step, and its earmark is a phrase containing, "I feel," "I believe," "I feel that my patients are helped," or "I believe the drug is doing good." This is the *sine qua non* to further developments. It is what has been called the retail point of view. One is concerned with the individual, accumulates a number of individual cases, and draws conclusions from a consideration of these cases. Without such a conviction one would never know what kind of exact tests to make or what things to look for when the drugs are administered. So there is no conflict between this and the other type of approach, that of the experimentalist and that of the statistician or actuary—the wholesale point of view. The experiments and statistics of the objective scientist are just as necessary in verifying a hunch as clinical art is necessary in its inception. I assure you that getting the right hunch is by far the more creative part of the job; but testing the hunch is by far the most important part and the one requiring the greatest expenditure of time and care.

My own impression from the papers, particularly on the clinical side, is that meprobamate does act strongly on what might be called symptomatically (I here may violate some *caveats* I made earlier) the tension level. This level helps control stress or decrease tension, whether in terms of lessened downward discharges to muscles and easing of spasticity, of lessened discharges upward to the cortex (or the psyche or superego) with an easing of hostility, directed outward or inward, of anxiety, or of some other factor.

Control of Tension Level

Enthusiasm over the action of meprobamate in making patients co-operative has been expressed in a number of papers. Senile, alcoholic, and other sad relics, who would not accept help from willing and friendly ward personnel, abandoned their stubborn resistance. This is obviously a good and helpful effect and indicates a valid use for any drug that can produce it. One could, however, as implied by Huxley, use another word for "co-operative." One could say the drug makes people docile, renders them susceptible to outer influences, including the "big brother" variety and brain washing. As Dickel asks, what are the criteria that one should consider in judging effective therapeutic results of a drug? They include not only the feelings of the patient,

but also his performance in the community, whether or not he can hold a job and interact with his fellows.

Two basic antinomies arise here: the conflict within the individual, between the desire for nirvana and the desire for experience; and the conflict between the individual and the group, for the peace of the individual and the progress of the society or species. As far as the group is concerned—and I should use here the term "epiorganism"—it is certainly true that, throughout evolution, selection of individuals to be parents for the next generation has had nothing to do with the welfare of those individuals. In most cases the selection has been an entirely painless one in terms of slight advantages in adaptive mechanisms but, in many situations, the individuals are ruthlessly sacrificed for the good of the group.

This is really the theme of the legend of Prometheus, who stole fire from heaven. He brought progress for mankind but, as an individual, he suffered the tortures of being torn by ravens. The conflict between the individual and the group also underlies the ethical problem in human experimentation that has been aired here. Is it ever ethically permissible to withhold from a patient that treatment which, at the moment, is regarded as the best and most satisfactory? If not, how could one test the new, or give placebos to controls, or try uncertain remedies? Conversely, under what conditions is it desirable or ethically permissible to try on a patient something that may be better than the current agent but which may also prove harmful? When does one stop using the good in an effort to achieve the better? This is a very basic ethical problem and it bothers all who operate in this field, not only morally, but even legally. It is not easy to answer the question: "What calculated risk is permissible with a given human individual for a potential great gain to mankind as a whole?" I do not presume to resolve this problem; I simply state it.

Turning, finally, to conflict within the individual, there are a number of interesting points. Consider the new techniques of allowing monkeys with indwelling electrodes in the brain to give themselves shocks. If the electrode is in a region associated with painful experience, an animal presses the lever once, jumps, and never touches it again. If the electrodes are elsewhere, however, in the limbic system and its adnexae, the animal is likely to continue punching the lever for long periods, and will even undergo some external discomfort in order to do this. The question arises "What does he get out of it?" There has been a tendency, with some justification for certain regions of the brain, to think that the shocks arouse the equivalent of sexual feelings; if such feelings can be produced centrally, without wearing out the peripheral mechanism, continuing elicitation is understandable. It may not be as simple as this, however; there is some reason to believe that, rather than pleasurable experience, the stimuli may give only nirvana. Children with *petit mal*, who can bring on an attack with a flickering light, may spend hours in the sunshine waving their fingers before their eyes and having attack after attack. They behave in many respects like the monkeys; conversely, the monkey behavior is perhaps directed to a negative effect. Are these animals seeking a positive pleasure or a negative absence of experience? Here, at least, is a technique only beginning to be exploited that may lead to many clear-cut answers to such questions.

More immediately I remind you that, both in the evolution of the species and in the development of the individual, with the increase of the functioning cortex there is a progressive emergence of what Kleitman called the wakefulness of choice as compared to the wakefulness of necessity. This goes back to W. R. Hess's experiments three decades ago. Animals sleep and are inactive except when they must do something about solving the problems of life. This is the wakefulness of necessity. With the growth of the cortex there is more and more of the additional wakefulness of choice—an extra libido; in Alexander's view, the play libido—a desire or the ability to keep going, to be active for activity's sake, a *joie de vivre*, a joy of play.

Huxley has made the point that all natural depressant drugs, tranquilizers or whatever one may call them, have been known from antiquity. This is certainly true. He did not suggest, however, that all the natural drugs that give increased activity, that move one away from a state of peace and nirvana, were also discovered in antiquity. Indeed, as far as I know, these are much more widely sought and used in every culture than are the depressants. As regards primitive or advanced groups, coffee, tea, or maté, wherever available, is the main beverage of the people; the cup that cheers takes precedence over the cup that inebriates. I have some apprehension at Huxley's suggestion that we try to teach children to control their autonomic nervous systems. It took organisms a long time to exclude these actions from voluntary control, so that the fools could not kill themselves off at once. By way of answering Huxley's concluding question, I rather suspect that, even though we are now tampering with the upper part of our nervous system, we shall survive without serious damage.

There is certainly something like an *élan vital* effective in all living creatures, pointed up in man as a "divine unrest." Biology would give a positive answer to the question that the poets and the humanists have raised and have answered in all possible ways and nuances. The biologist stands with Louis Untermeyer rather than with Swinburne, and therefore subscribes to the second of these verses:

"From too much love of living,
From hope and fear set free,
We thank with brief thanksgiving
Whatever gods may be
That no life lives for ever;
That dead men rise up never;
That even the weariest river
Winds somewhere safe to sea."

"From compromise and things half-done,
Keep me, with stern and stubborn pride;
And when, at last, the fight is won,
God, keep me still unsatisfied."

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