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Chemistry of the Brain

Past Imperfect, Present Indicative, and—Future Perfect?

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Only 30 years ago a prominent neurologist, while discussing with me the future of neurochemistry, referred to it as the chemistry of "brain hash." For him, neurochemistry had no more attractiveness than the chemistry of any other hash. As far as he knew, the brain had no organized chemical mechanisms; it consumed no oxygen and evolved no carbon dioxide, or did these things only incidentally. His mind was concerned wholly with tracts and lesions. Yet this was at a time when the chemical relationships of other organs were well established. But the nervous system was maintained in splendid isolation, almost as though there were unconscious fears that the rude attack of scientists carried with it the seeds of self-destruction. And we shall see that there may be some truth in this premonition.

J. L. W. Thudichum many years ago initiated work on neurochemistry, oddly enough at the instigation of his government, to determine the effects of typhus on the brain. His was an amazing career of scientific productivity that I have described in my first book on the *Chemistry of the Brain* (*1*). Thudichum thought well of his work, for he said, "In order, however, that the reader may not, from this avowal, come to any erroneous conclusions regarding my own estimate of the value of my researches communicated in this treatise, I undertake to assure him that they are of fundamental importance, and that all further developments in chemical neurology must start from them as a basis." And, in a way, Thudichum was right.

But the flame died; clinical neurology and Freudian psychiatry took over and nothing was heard of either Thudichum or neurochemistry until the 1920's, when workers in this country began to prove that nerve tissue had indeed a metabolism. The necessity to prove this seems naive and strange in retrospect, but people were greatly imbued with the implications of the analogy between transmission of an electric current over a copper wire and transmission over nerves.

By 1923 Kraepellin had expressed the wish to have a department of brain chemistry in the projected Kaiser Wilhelm Institute for Psychiatry in Munich, and in 1928 I had the fun of implementing the concept. This was, I believe, the first modern laboratory devoted wholly to the chemistry of the brain. There were, of course, many other laboratories in which various projects concerned with nerve tissues had been investigated. In England, Quastel was beginning his fine work. But somehow, our efforts failed to fire the imaginations of either investigators or clinicians until around the early 1940's, when Gerard, Elliott, Himwich, von Euler, McIlvain, and their like appeared, along with some strong encouragement from other fields of endeavor. The anticonvulsants, chemical transmitters of nerve impulses, tranquillizers, lysergic acid diethylamide, and serotonin all contributed to the red glow of incipient intellectual combustion. The chemical mechanisms of the brain were no longer to be denied; the era of the subjective was being crowded and complemented but not replaced by an era of the objective. The movement was long overdue and illustrates how a method such as psychoanalysis, for example, no matter how worthy in itself, if followed to the exclusion of other investigative facets, seriously hampers development of a discipline.

What I have to say is merely illustrative of the "past imperfect, present indicative, and—future perfect?" My purpose is to examine a field of endeavor that is not yet fully formed in the hope that adumbrating its lines of growth may facilitate and better its development.

Control of Arterial Pressure as a Neurochemical Function

Many of the functions of the body that are maintained homeostatically are in part, but seldom wholly, under the control of the nervous system. Normal arterial blood pressure is a good example. The vasomotor centers in the medulla seem to control it almost completely under ordinary circumstances. This does not mean, however, that these centers alone control blood pressure and cardiovascular reactivity—that is, the degree to which the cardiovascular system responds to vasoactive drugs.

In Fig. 1 I have oversimplified the problem for the sake of stressing the principle involved. Note that the vasomotor centers are subjected to a variety of controlling mechanisms, most of which may be chemical. Psychic functions may have a profound effect on these centers, but the mechanisms by which they act is quite unknown. There is a certain "guilt by association" in the effects on blood pressure of the disease called acute porphyria. I remember very vividly a patient we studied who had this disease, especially because for more than a year we misdiagnosed her disease as essential hypertension with conversion hysteria. She was an example of a neurotic girl at her worst, and that can be pretty bad. But she had sufficient hypertension to keep our interest. Things went from bad to worse in the hospital until finally, after bouts of convulsions, temper tantrums, and altogether bizarre behavior, she was dismissed. The correct diagnosis was made by chance in another

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hospital, so often referred to sneeringly as "elsewhere." I say by chance because a sample of urine was allowed to stand for hours before it was sent to the laboratory, and during this period of inefficiency it turned deep red. When the porphyria spontaneously cleared, possibly because no more barbiturates were given, the girl almost miraculously became a thoroughly well-adjusted and nice person; her hypertension disappeared. Was her case an effect of the upset porphyrin metabolism on the psychic functions of the brain? Or was it an effect directly on the brain itself and on the autonomic system which affected both her behavior and her arterial pressure? Possibly hypertension is the result of direct action of porphyrins on the smooth muscle of blood vessels. I do not know the answer, but the problem is an interesting one and suggests that Klüver's finding (*2*) of porphyrins in the central nervous system needs much more penetrating study.

It is believed that the vasoconstrictor centers are to some degree influenced by the access to them of humoral agents such as adrenaline and acetylcholine, drugs having a "central action." Curiously, these drugs often seem to have quite the reverse effect than they do when they are injected peripherally: adrenaline causes a fall in arterial pressure when it is injected into the cerebral circulation, and acetylcholine causes a rise. I have no idea how important this mechanism is in the control of normal blood pressure.

Another aspect of the problem of the interrelationships of blood-borne substances and neurochemical reactions is the chemical environment of the vasomotor centers. The chemical environment to a considerable degree determines the intensity of the responses of the centers. The *p*H and carbon dioxide concentration are among the better recognized environmental factors, but there must be many, many others which not only provide for the well-being of the brain tissues but also determine their ability to respond.

Perhaps the most important neurochemical control of blood pressure is mediated by the buffer reflexes. These reflexes, in turn, seem to be initiated either by distention of the arterial wall (baroceptors) or by the chemical composition of the blood (chemoceptors). The distention of the arterial wall is in itself determined not only by the height of the blood pressure and the character of the pulse wave but by a variety of chemical agents that affect distensibility. I shall not pursue the matter further, lest I inadvertently stray back into the fields of arteriosclerosis and hypertension, from which I make my living. But let me press the point that the control of these vital functions of the body, blood pressure and tissue perfusion, is, in the final analysis, largely neurochemical.

Neurosecretion

The secretory function of the brain is in one way well known and in another way almost unknown. Most scientists are familiar with the fact that adrenaline and noradrenaline are secreted by nerve tissue and that the hypothalamic-pituitary system secretes and stores hormones. But there the thinking stops, and any suggestion that the brain has as one of its functions secretion of hormonelike materials is usually met with broad skepticism. Let us look at some of the evidence that supports the suggestion of neurosecretory action.

Hormones, including molt-inhibiting, metabolic, and chromatophorotropic hormones, are present in parts of the central nervous system of crustaceans (for review, see B. Sharrer, *3, 4*). Some of these hormones are secreted by the neurosecretory cells of the x-organ and transported through the axons of the cells to the sinus gland for storage.

Neurosecretion was first demonstrated in the nucleus preopticus in teleostome fish and subsequently has been found also in reptiles, birds, and mammals. The secreted material from the hypothalamus is transported to the neurohypophysis via the axons of the neurosecretory cells that terminate in the pituitary stalk and in the pars nervosa. The endings in mammals often appear as bulbous swellings known as Herring bodies.

The work of the Sharrers (*3*) has largely established the concept that, both in vertebrates and invertebrates, neurosecretory cells have the dual role of neurons and glands. In vertebrates, however, the secure evidence is so far limited to the neurosecretory cells in the hypothalamus and their relationship to the pars nervosa; the hypothalamus appears to secrete vasopressin and the pars nervosa to store it.

One of the more fascinating observations is that severance of the autonomic recurrent nerve in the insect, *Leucophaea,* results in development of tumors in the organs innervated by this nerve, notably the anterior portion of the gastrointestinal canal (Sharrer, *4*). Stomach tumors account for the majority of deaths following nerve section. The evidence is clearly in favor of the theory that the nervous system can act as a secretory system having important effects on the body.

Another example of a substance released by secretory activity may be "cerebrotonin." We think we have shown that cerebrotonin is released from the brain when the central end of the cut vagus-sympathetic trunk is stimulated electrically (Taylor and Page, *5*). This vasopressor material seems to be different from all known hormones. It has not yet been identified, nor has its site of release been determined. If this substance is physiologically active, and is not vasopressin, it would provide yet another method for the control of vasomotor tone by the brain. Although we have no evidence to suggest that it does so, it is the sort of substance that could help, in part, to maintain blood pressure at relatively normal levels after section of the spinal cord and vagus nerves.

But these are only examples of the important possibility that the nervous system does more than exert control by means of transmitted nervous impulses; it can also regulate directly through chemical secretion produced by nerve cells. This aspect of neurochemistry has received little attention.

Autonomic Representation

It is odd that so far we have learned a good deal more about the chemical events in the autonomic nervous system than we have about events in other parts of the nervous system. We are not at all sure, for example, why transmission within the brain seems less easily blocked by atropine or hexamethonium than transmission across autonomic ganglia. Let me give just a few examples of what I mean.

Largely through the work of Ulf von

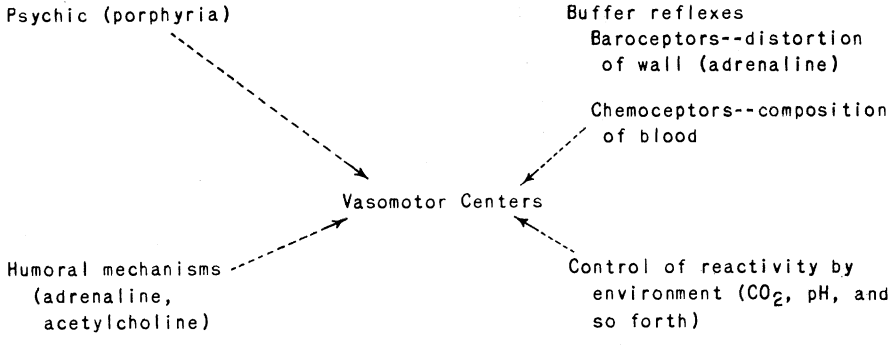


Fig. 1. Control of arterial blood pressure as a neurochemical problem.

Euler, it has been shown that noradrenaline is liberated at adrenergic nerve endings and that adrenaline is liberated as well, in some cases. Recently Peter Holtz (*6*) has shown that a decarboxylase exists in nervous tissue which decarboxylates 3,4-dihydroxyphenylalanine to hydroxytyramine, thus providing the building material, or precursor, for synthesis of noradrenaline within the nervous system itself. But note that it is present in highest concentration in postganglionic sympathetic nerves and that almost none is present in cortex.

Vogt (*7*) found high concentrations of sympathin in the hypothalamus and the area postrema, less in the midbrain, and still less in the medulla and medial thalamus. It was found nowhere else. Clearly, the sympathin content was associated with the central representation of sympathetic activity. In cats, 7 percent, and in dogs, about 14 percent of the sympathin is adrenaline and the remainder noradrenaline. Vogt's suggestion is that sympathin is the adrenergic activator of secretion by the anterior pituitary, chiefly because drugs that stimulate these centers reduce the content of sympathin.

The content of substance P, a smooth muscle stimulator of polypeptide structure discovered by von Euler and Gaddum (*8*) and extensively studied by Pernow (*9*) parallels the content of acetylcholine except in the hypothalamus, which shows the highest concentration of substance P. According to MacIntosh (*10*), still another substance, acetylcholine, is found in highest concentration in the basal ganglia and midbrain of cats.

Serotonin is also found in the brain in relatively high concentration. It has, like so many other substances, been suggested as a transmitter. Its distribution in brain is not unlike that of noradrenaline (Amin, Crawford, and Gaddum, *11*) and may therefore be associated with central autonomic representation. But Twarog (*12*) suggests that serotonin has a specific inhibitory action to acetylcholine in *Mytilus* muscle. Marrazzi and Hart (*13*) found serotonin 6 to 8 times as potent as lysergic acid diethylamide and 30 times as potent as adrenaline in ability to inhibit cerebral synaptic transmission. As a neurohumoral inhibitor, serotonin might be very effective.

Histamine is found principally in postsynaptic sympathetic fibers, according to von Euler (*14*). In the brain, its concentration is high only in the cerebellum and hypothalamus. Histaminergic synapses have not been demonstrated so far.

The hypothalamus thus seems to be the "*Beilstein*" of the brain, containing, as it does, the highest concentrations of noradrenaline, serotonin, substance P, and histamine; it contains acetylcholine, adenosine triphosphate, and vasopressin as well.

There seems to be among the physiologically active substances a certain economy of function such that a relatively few substances have a great variety of actions. The catechol amines, widespread throughout the body, not only mediate sympathetic transmission and affect importantly the carbohydrate metabolism but, in addition, they, or their degradation products, seem to affect psychic function. Serotonin and other indole derivatives seem likewise to exert multifaceted actions, and less could not be said for histamine and, possibly, substance P. It is this multiplicity of action combined with the economy of molecular species that makes the semi-isolated brain a chemical kingdom largely sufficient to itself.

In connection with autonomic representation, I want to mention again the problem of inhibition of transmission within the brain, for many of these substances have this property. Marrazzi and Hart (*13*) first pointed out that a variety of adrenergic substances inhibit synaptic transmission. Later they found serotonin to be the most powerful inhibitor of all the substances tested. From this they suggest that some forms of mental disturbance result from an imbalance between serotonergic and adrenergic inhibition and cholinergic excitation in the more susceptible cerebral synapses. Inhibition of the transcallosal potential was found by Slocombe, Hoagland, and Tozian (*15*) to parallel diminishing spontaneous electric potentials resulting from serotonin in rat's brain. The effectiveness of the inhibition under Pentothal anesthesia was in the following order: serotonin, lysergic acid diethylamide, adrenaline, noradrenaline, and last, adrenochrome. Slocombe, Hoagland, and Tozian suggest that these drugs have a common mode of action. Quite recently Bazemore, Elliott, and Florey (*16*) have isolated what appears to be Florey's factor I, which is believed to be a transmitter substance of inhibitory neurones. Interference with its action may be the basis of the convulsive effects of some drugs. At least part of the action of factor I seems to be due to γ-aminobutyric acid. This acid had previously been found in brain; it is produced by the action of a decarboxylase on glutamic acid.

Psychotomimetic Drugs

Drugs that produce mental disturbances have been known since the dawn of history, but it is only recently that they are being studied from the point of view of their actions in terms of chemical mechanism. Former observers, of whom there were many astute ones, were content to record the effects of the drugs but showed no concern for their chemical pharmacology.

There is no need here to review the subject. Instead I shall select lysergic acid diethylamide as a prototype, because of its ability, even in minute quantities, to produce mental change, and because suggestions have been made to explain how it acts.

In a way, this story began with the isolation and determination of the structure of lysergic acid by Walter Jacobs and Lyman Craig in 1936. I was working at the Rockefeller Institute for Medical Research when this was done and remember being told about the project by Craig as we were going onto the tennis court one day, which proves the value of tennis courts over convention halls as a means of communication. A. Stoll and A. Hofmann in 1938 synthesized *d*-lysergic acid diethylamide, but it was not until 5 years later that Hofmann noted (*17*) on Friday, 16 April 1943, that, "I was forced to stop my laboratory work in the middle of the afternoon and to go home, as I was overcome by a peculiar restlessness associated with mild dizziness. Having reached home, I lay down and sank into a kind of delirium which was not unpleasant and which was characterized by extreme activity of the imagination." Hofmann had accidentally ingested some lysergic acid diethylamide. He was scientist enough to suspect, and later prove, the relationship between the substance he was working with and the hallucinations. In 1947 W. A. Stoll (*18*) reported a careful, psychiatrically oriented study and so began the story of a drug that is having a profound effect on modern psychiatric thinking.

The amount of some substances required to affect thought is so minute that concern with quantum effects is suggested. A substance like lysergic acid diethylamide elicits profound psychobiological actions, according to Axelrod, Brady, Witkop, and Evarts (*19*), when concentrations of the order of 0.0003 micrograms per gram of brain tissue are administered; the necessary concentration is probably lower than this since the substance is rapidly metabolized (Stoll, Rothlin, Rutschmann, and Schalch, *20*). In the mouse the half-life is only 7 minutes. If quantum effects are, in fact, involved, it follows that understanding itself will be subject to the same indeterminacy proposed by Heisenberg for quantum mechanics.

Another part of the story begins with the discovery of serotonin (5-hydroxytryptamine) in 1947 and the demonstration, both in this country and in England, that it is present in very considerable amount in brain tissue. Wooley and Shaw (*21*) subsequently synthesized a number of competitive antagonists to

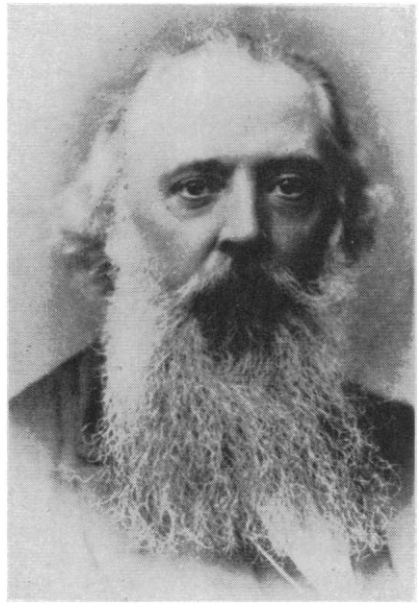
serotonin and, on the basis of the actions of the antagonists and of the harmala alkaloids, made the shrewd suggestion that serotonin might be concerned in mental disease.

In 1954 Gaddum (*22*) showed that lysergic acid diethylamide is a powerful antagonist of serotonin's action on the uterine strip and also suggested that the concentration of serotonin in the brain had much to do with maintaining normal mental functions. Serotonin might thus be an antagonist for hallucinations caused by lysergic acid diethylamide. Actually, administered serotonin does not appear to cross the blood-brain barrier, hence could not be expected to be effective. Even so, there is evidence that it is not a simple antagonism, for Rinaldi and Himwich (*23*) have shown that azacyclonol, α-(4-piperidyl-benzhydrol) abolishes the electroencephalographic changes produced by lysergic acid diethylamide in rabbits. Further, more recent work has shown that azacyclonol is effective in patients that have been given lysergic acid diethylamide and in eliminating the hallucinatory phenomena during acute schizophrenia (Fabing, *24*). Clearly the actions of lysergic acid diethylamide on mental phenomena are many sided and highly complex. Nonetheless, the intellectual ice has been broken and the problems of neurochemistry are taking form. This is the beginning of progress in research.

There followed a series of important papers by Brodie and Udenfriend in which it was shown quite conclusively that reserpine causes the release of the bound serotonin in brain, enabling it to be destroyed later by amine oxidase. Serotonin is believed by Brodie and Udenfriend to be the intermediary for the tranquilizing action of reserpine.

Reserpine has a prolonged action, yet actually disappears from both plasma and brain shortly after its intravenous administration. According to Hess, Shorr, and Brodie (*25*), it achieves a maximum level in the brain in about 15 minutes. Its effects are related temporally to change in serotonin, and they seem to be a consequence of this change. The primary action of reserpine is suggested by them to be impairment of the capacity of cells to bind serotonin. The free serotonin, even though it is low in concentration, is presumed to exert sedative and other effects that persist until the cells regain their capacity to bind serotonin.

Serotonin itself does not appear to cross the blood-brain barrier and it is not known whether the serotonin within the brain is exogenous or endogenous, or both. Udenfriend, Bogdanski, and Weisback (*26*) have partially solved this problem in a very ingenious way. As they showed earlier, 5-hydroxytryptophan is converted to serotonin by a specific decarboxylase that is found in many mammalian tissues. Administration of this amino acid resulted in the appearance of serotonin in such organs as liver, kidney, heart, and uterus, which normally contain none. Since 5-hydroxytryptophan penetrates the blood-brain barrier, a marked increase in brain serotonin occurs. In animals, it was possible to raise cerebral serotonin 20-fold. Of great interest is their observation that the effects at these high levels resemble those seen after administration of lysergic acid diethylamide.



J. L. W. Thudichum, founder of neurochemistry.

Just as in all research problems, difficulties have recently arisen that throw doubt into this boiling scientific cauldron. Bromolysergic acid diethylamide was synthesized in the Sandoz laboratories. In a way, this was too bad, for it has provided these doubts. As closely related structurally as it is to lysergic acid diethylamide, it produces little mental disturbance except in very large doses. It has been said that it produces none at all, but two of our staff physicians at the Cleveland Clinic have taken 5 to 7 micrograms per kilogram, per minute and found that it elicits slight mental aberration, though nothing like that produced by lysergic acid diethylamide. Thus, as shown by Cerletti and Rothlin (*27*) in Basel, we have the curious phenomenon that the substitution of one atom of bromine profoundly alters the molecule's effect on the psyche. But even more difficult is the fact that the bromo lysergic acid is an even more potent antagonist of serotonin on the uterus than lysergic acid diethylamide, as my associate from Brazil, L. Sollero, has found (*28*).

Another interesting phenomenon of relevance is that the hypnotic effect of barbiturates is potentiated by serotonin and by reserpine. This phenomenon has been studied especially by Shore, Silver, and Brodie (*29*). These potentiations are blocked by lysergic acid diethylamide. Despite their differing effects, lysergic acid diethylamide and its bromo derivative both block the potentiating effects of serotonin and reserpine (Salmoiraghi, Sollero, and Page, *30*). Introduction of a bromine atom into the molecule of lysergic acid diethylamide thus enhances the serotonin-blocking activity on smooth muscle, but it does not alter its antagonism to serotonin in the central nervous system. Catechol amines have an action similar to that of serotonin in enhancing the action of barbiturate hypnotics.

The problem of the function, if any, of serotonin in brain is far from solved. Its importance currently has been to provide, along with lysergic acid diethylamide, a nidus around which thinking about chemical reactions and the psyche revolve. It is such approaches as these that will, in my view, provide many of the keys to the solution of the problem of mental disease. It has taken phenomena as well as substances of this sort to make neurochemistry real. As I certainly had occasion to know, it was a never-never land until their advent. I personally could not wait, so I took up heart disease as a way to feed my family. In most ways I do not regret it.

I feel impelled at this point both to encourage and to scold the young investigators in this field, especially those coming from the psychiatric disciplines. With the recent acceptance of the principles of neurochemistry has come a wave of uncritical enthusiasm which, if allowed to go unhampered, will almost inevitably lead to grave disillusionment. Without mentioning any names, let me single out one recent episode to illustrate. First comes a highly imaginative and singularly well-written article pointing out, not only the structural similarity between one psychomimetic drug and one not known to have such properties, but also that, on administration of the latter, it was found to be, in fact, psychomimetic. Soon it was heralded as a cause of schizophrenia. Almost inevitably, several serious difficulties have arisen. Others have not been able to repeat the observations, possibly because the substance used originally was not properly defined chemically. Many substances are now being resurrected that are psychomimetic but have no structural similarity. And finally, there is so far no evidence that abnormality in the metabolism of this *x* substance causes schizophrenia.

This is simply to point out that psychiatric research of the chemical sort must, as I have tried to point out before

(*31*), go the long, hard way. No matter how well meaning and how stimulating some of the recent theories may be, we must not get overstimulated in order to forget the hard road under foot. Although, again, I should not single out special cases, I am bound to say that I like the careful approach of the Hoagland group at the Worcester Foundation for Experimental Biology. I do not know whether their view of the great importance of the adrenal glands in the genesis of mental disease is valid, but I do know that their basic research on the problem of adrenal chemistry in relation to neurochemistry will ultimately yield rich dividends. Careful, penetrating investigation, no matter how oriented, has always enriched the value of the world's intellectual stock.

Piperazine Derivatives

I have chosen the piperazine derivatives chiefly because we have recently studied a few piperazine derivatives in both animals and patients, especially 1-(2-methoxyphenyl)-piperazine monohydrochloride. This substance has some antihypertensive properties, but tolerance develops too soon for it to be used as a practical remedy.

It soon became apparent, in the hypertensive patients who received the drug in doses of about 400 milligrams per day, that its effects on the brain were more interesting than its effects on blood pressure. After single intravenous doses, the patients became drowsy or somnolent for about 12 hours. The same result occurred early after oral administration, but in addition, after 2 or 3 weeks of medication, bad dreams occurred regularly in persons who had hitherto been unaware of dreaming at all. In some patients, the dreams were so frightening that the patient became very fearful of going to sleep. While mental confusion and lethargy often occurred, the almost specific nightly experience of dreams was the conspicuous feature of this syndrome.

I have studied the effect of this drug on the arterial pressure responses to a variety of pressor agents in animals. Its most characteristic action is a powerful blocking of phenylalkylamine drugs such as ephedrine, amphetamine, Aramine, Neosynephrine, and Aranthol; it had relatively small effects on adrenaline, noradrenaline, cobefrine, and angiotonin. There is then a mere suggestion that this piperazine derivative might exert its central nervous action by blocking this particular group of phenylalkylamines. I must stress, however, that this type of suggestion may be very misleading without further evidence for such an association.

Other piperazine derivatives have tranquilizing effects and have found important application in medicine, while still others seem to be able to stimulate sympathetic ganglia powerfully. One of the latter is 1,1-dimethyl-4-phenylpiperazinium iodide. Piperazine derivatives, in my opinion, deserve much closer study from the viewpoint of their effects on the chemistry of the nervous system.

The Mind and Neurochemistry

The nature of mind is no clearer today than it was when the problem was propounded by the early philosophers. Much fruitful speculation, and indeed experimentation, has been carried out under the "switchboard" concept of brain function. But the jump from making the switchboard more and more complex until reason appears is one I find difficult to make. Sensation and thought, for example, do not seem to me to be equivalent.

But many must disagree. For example, in a recent article in the *Atlantic Monthly*, G. R. Harrison (*32*) states, "The more flexible electrochemical processes we call thought take place in the new brain, a vast set of switchboards located in the cortex of the cerebrum." Again, ". . . all the glorious welter of color, sound, and emotional involvement of our world results from countless tiny pulses of electricity, and all instinct and awareness appear to be the result of their combinations." And even with assurance he states, "The circuits of the mind improve vastly with use and exercise. Thinking in a given way brings an increased blood supply and more nourishment to the cells and synapses involved." I am not aware of the proof on which these statements are based.

What impresses me more is the confidence many physicists show in their ability to solve the age-old problem of the nature of thought. Feedbacks, cybernetics, molecular memories, and so on are indeed impressive concepts, but so far they carry no conviction to me. The brain is no more than a physical mechanism which, without the mind, is not unlike the so-called "electronic brains" of industry. But without the guiding mind, the brain comes to little. This is not a problem to be approached lightly, for the worlds of belief, of faith, of beauty, and of happiness are at stake.

A materialistic science may not have the methods requisite to the analysis of such a problem. Science has failed before because the problem did not lend itself to analysis by the tools of science, and it can do so again.

Having said this, I now feel free to look more closely at something that is tangible and that is subject to analysis by the usual methods of science. Scientists have been peculiarly reticent about investigating the chemical nature of the brain. It must have occurred to many to do so. What could be more fascinating than to understand something of what goes on in one's own head? Something has held progress back: whether it is the evanescent nature of thought, the Freudian approach, or some vague concept that the brain had no metabolism, I do not know. Certainly, psychiatrists have shown little relish for the mechanistic approach. Curiously, the neurologists have been little better. They have been content to study reflexes and describe syndromes with little concern for the mechanisms of disease which underlie disease. Surely they all knew that adrenaline was a chemical

Deutsche Forschungsanstalt für Psychiatrie, Kaiser Wilhelm Institute, Munich, Germany.

which reproduced the results of sympathetic nerve stimulation and that transmission over ganglia is a chemical process. This ought to have been enough to have made them curious about other chemical processes within the nervous system. But not so; until very recently almost nothing has been done in this country at least to further the discovery of such knowledge.

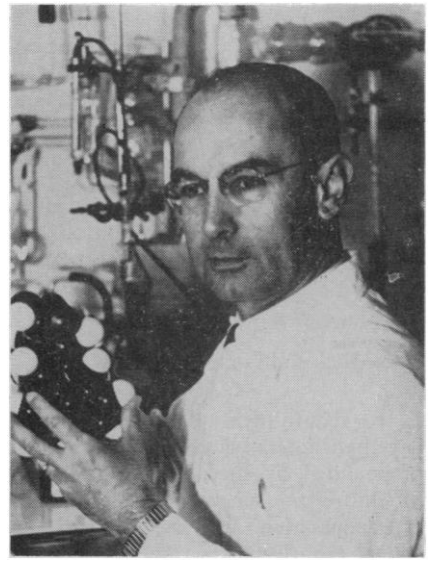
The mind-body dualism has received no solution, but at least it is under investigation. Whether mind is only another property of that remarkable stuff called protoplasm, or whether it is an intangible stuff not lending itself to such material approaches as those of science, will be answered eventually; the point is that the search has started. Whether the brain secretes thought or is only the substrate that provides the means of expressing it is another of the persistent problems. But the least common denominator is that the nervous system requires energy which is chemical, and this is subject to scientific analysis. If we are content to do this competently, a great contribution will have been made.

The recognition of the problem has been a long time in coming from when it was first dimly posed by Thudichum. Thudichum himself was a prophet without honor in the eyes of others. But even in our country there has been little ready acceptance. Biochemists in this country have taken notice of it only in the past ten years at most, and psychiatrists and neurologists in the past three years. The primeval beginnings are still with us.

The close chemical interrelationship between the brain and the body seems to be one that is hard to grasp. Somehow the brain has been dissociated from the body in people's thinking. For this reason, it comes as a surprise that disturbances in brain function can result from diet and that this disturbance may be reflected in chemical disturbances in urine.

For example, Rodnight and McIlwain (*33*) find that the depressive or manic depressive psychosis of pellagra is associated with persistent indicanuria. There seems to be a good basis for associating nicotinamide deficiency and indicanuria because tryptophan can serve as precursor not only of indican but also of nicotinamide. They suggest that indicanuria may represent a diversion of tryptophan from a more essential metabolic route, making the individual more in need of dietary nicotinamide. Another important pathway of tryptophan metabolism is through the formation of serotonin.

Still another interesting example is the metabolic phenomenon of phenylketonuria (phenylpyruvic oligophrenia), in which mental deficiency is associated



Albert Hofmann, the discoverer of the action of lysergic acid diethylamide [Courtesy of R. Bircher, Sandoz Pharmaceuticals]

with an inherited abnormality in the metabolism of phenylalanine. Improvement has been reported in the behavior of patients following use of a diet restricted in phenylalanine. The restriction results in lowering of the high levels of phenylalanine in the blood.

It Could Be Philosophy

It has always seemed to me that the chemical approach to the brain is shunned, perhaps among other reasons, from an unconscious fear that is casts doubt on the religious nature of man. My own experience has shown this to be true from the number of unsolicited letters I have received from priests and ministers of all levels of intellectual sophistication, as well as from the public, when my book on *The Chemistry of the Brain* first appeared a good many years ago. Some of these have been inquiring or humble; many have been critical or downright abusive.

The fear must stem from what seems to be a current trend in the direction of dialectical materialism—a trend, I might add, that is at the basis of much anti-intellectualism and animosity toward science. Science has not given man happiness; that is fairly certain. It is a question in a few people's minds just how much it has even improved things. Noble impulses have not followed automatically from the leisure time created by technology.

Science has lost the public mind in a maze of facts and, with them, their inner meaning. Materialistic naturalism is currently prevailing among many of our people as a result of science. This results in a much stronger case for communism than for our free way of life. If man is created entirely materially, then freedom of will has no meaning. If man is wholly a product of natural law, then individual freedom is surely an illusion and the philosophy of communism is a much better solution for his problem than a system that urges a freedom which cannot, and should not, exist.

I wish I knew the solution to this vexing problem of the impact of a materialistic science on the peoples of the world. We can all agree as scientists that it is our prerogative to go as far as is possible with whatever scientific device we know. That prerogative we must never surrender. As scientists, our philosophy of life is no better than that of other thoughtful people, and in some cases it is a good deal worse because of our lack of experience in the much more populous world of intuition and value judgment.

By study of the chemistry of the brain, we seek to define the mechanisms that result in the transmission and integration of nerve impulses and, concurrently, to define their association with thought, no matter what association that may be. The danger quite obviously lies in the nature of the problem of thought itself.

Thought can be influenced by chemical reactions, and it seems to be able to influence them in turn. Thought has been called a property of protoplasm just like any other property, robbing it of its uniqueness. Indeed, as scientists, we go to no little trouble to convince ourselves that thought is just as subject to scientific method as other natural phenomena. It is disturbing to think that it might not be. As a scientist I must confess that, so far, there has appeared not one shred of evidence that it is. I think also that I see more and more circumstances suggesting that it is not subject to methods of analysis as we now know them and to the reproducible experiment.

Might it not be that in this problem we are approaching the ultimate where the same type of problem of causality arises as occurs in the case of the quantum theory and the uncertainty principle? Even measurable data have lost their absolute certainty in this case. But how do we even measure values and emotions that constitute much of the world in which we live?

Is science, as Francis Bacon thought, an image of truth or, better, reality? It is constituted of sense experience, and as neurochemists we should immediately be warned. Sense experience acts as a transport mechanism separating us from reality and possibly correctly informing us of it. Only the images of reality formed and transmitted by the tenuous thread of the nervous system reach consciousness. How close do they mirror

absolute reality? Ask yourself what conception you would have of reality and science if you had been born with a continuous supply of lysergic acid diethylamide.

Scientists are likely to forget that they operate on faith exactly as do religions. Particularly relevant is the fact that the acceptance of any system of logic for thinking about our own sensory experiences is an act of faith. As Vannevar Bush (*34*) puts it, "Our reasoning appears sound to us only because we believe it is and because we have freed it from inconsistencies in its main structure; for it is built on premises which we accept without proof or the possibility of proof."

Pure determinism leaves no place for chance. The configuration of the present moment uniquely and completely determines all the future. My thoughts and actions tomorrow are completely specified by nothing more than the present instant positions and velocities of a myriad of particles of matter and of energy.

I conclude with the hope that, for the small part we play in the shaping of things to come, the neurochemist will pursue his science to its utmost but will never forget that the problem of dualism of body and soul may not be solved in material terms only, and that on its solution hangs the fate of society. The problem must be approached humbly and with care lest ineptitude lead us into the greatest of human tragedies—a philosophy of nothingness; a philosophy without beauty; a philosophy without God. I personally see nothing to persuade me that the functions of the brain are not the functions of protoplasm and that these functions encompass both the material and the transcendant; that there is the necessity to include in the philosophy of biology both those material attributes which are our science and those immaterial attributes which are our values. It is the amalgamation of the two that will close the abyss, which has so destructively separated science from humanity as to make it appear the enemy of man and the enemy of God. In our hearts we know it is neither.

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W. Kaempffert, Science Popularizer

The death of Waldemar Kaempffert, on 27 November 1956, at the age of 79, brought to an end a distinguished career dedicated to the popularization of science. This included 26 years as science editor for the *New York Times,* preceded by a period of equal length as editor and free lance writer of popular science articles. He was one of the first, if not the very first, who made the whole field of science his domain, and one of the very few, and for a considerable time the only one, who could write with authority on developments in all major fields of science, from astronomy to zoology, with clarity and simplicity yet without sensationalism or distortion.

In this respect he set the standards for the modern art of science writing, of which he was for many years the recognized dean. He was the first of the science popularizers who succeeded in making the ever-increasing flow of new-found facts of nature interesting to the lay reader, setting an example on how to steer a clear course between technicality and vulgarization, never bewildering his reader by talking over his head or patronizing him by talking down.

"It is the business of the journalist," he wrote in 1935, "to present the discoveries of the laboratory so that the many will understand. But Heaven forbid that the popularizer should rely too much on emotion. We have passed the stage when gaping wonder can pass for popularization. The facts, simply, humanly and interestingly presented, are what the public wants."

Waldemar Kaempffert was born in New York on 23 September 1877. His parents, Bernhard and Juliette, were of German descent. He graduated at the age of 20 from City College, where he majored in science and was elected to Phi Beta Kappa.

Upon graduation in 1897 he obtained a job as an assistant editor of the *Scientific American,* while at the same time he studied law at New York University. He won his law degree in 1903 and was admitted to the bar, but he never practiced. In 1911 he was named managing editor of the *Scientific American,* and after 4 years at that post he joined the *Popular Science Monthly* as editor, holding that position until 1920.

For some years after 1920 Kaempffert was a free lance writer on popular science. In 1927 he joined the staff of the *New York Times,* for which he wrote a weekly column on current research, occasional editorials on scientific subjects, and sometimes covered scientific conventions and other news events in the field of science.