

# NERVOUS AND MENTAL DISEASES AND THE NEWER PATHOLOGY

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The time, it seems to me, has arrived when it is possible to assemble and to weigh as to their significance numerous important facts bearing upon the pathology of the nervous system. In order that we may view these facts intelligently, it is necessary first to dispose briefly of the following preliminary considerations. To begin, nervous diseases are quite commonly divided into organic and functional. This distinction possesses a certain amount of practical value, but when analyzed it proves in its essence to be neither valid nor scientific. An affection which is attended in its early stages by no organic changes whatever may in a later stage be attended by changes gross in character. A notable instance of this is paresis, the symptoms of which may be pronounced in the early stage and yet this early stage reveal not the slightest structural change in the nervous system. Again, a broad distinction is habitually made between nervous diseases on the one hand and mental diseases on the other. While this distinction has in its turn an undisputed practical value, it likewise proves upon analysis to be invalid. This is shown by merely a cursory examination of the facts. Thus, it is well known that epilepsy may in addition to, or in place of, the gross nervous phenomena which it ordinarily presents, also present mental phenomena, and, indeed, often to such a degree as to necessitate its being classified among the insanities. A similar truth obtains in regard to hysteria, and when we turn our attention to its congener psychasthenia, we at once recognize that we are dealing with an affection which is still, in large part, in the domain of

nervous diseases and yet frankly occupies a place among mental diseases. Similar truths obtain in regard to melancholia and mania, and dementia præcox and paranoia, and, indeed, to mental diseases in general. The latter are, properly speaking, in this sense, merely functional nervous affections and must be embraced in any inquiry dealing with the pathology of the latter.

The facts which I am about to present in such an inquiry are facts which deal with material things. This truth cannot be sufficiently emphasized. The facts deal with changes of structure and function, with problems of metabolism, intoxication, infection, with questions of biochemistry and with other matters, all of which are identical in their nature with those which confront us in internal medicine. It is a remarkable fact that for years past many alienists have turned their attention to psychology rather than to internal medicine, the facts of which though of ever increasing importance have received but scant attention at their hands. The day however has gone by when we can be content with explanations of psychology and least of all with those of that now fast vanishing cult psychoanalysis.

All of the phenomena presented by the human organism, digestion, nutrition, the maintenance of the bodily temperature, the elimination of nervous and muscular energy, are convertible into terms of tissue chemistry. It is the summation of these manifold and complicated chemical processes that constitutes that moving aggregate which we recognize as the living individual. It is the derangement of these processes which constitutes disease,—a derangement which may have its origin spontaneously in some fault of the organism or which may be secondary to some cause introduced from without, such as a poison or infection. The metabolism of the body in health is as yet, it must be admitted, very imperfectly understood; notwithstanding there can be no doubt that its disturbances entail states of intoxication, and in these states of intoxication must be sought the pathology of mental and nervous disorders. Theories of autointoxication are as old as Hippocrates. In modern times they were advocated by Pinel, Esquirol, Morel, and others, though these older psychiatrists were inclined to regard states of intoxication as secondary to a primary affection of the nervous system. Numerous subsequent observers, among whom should especially be mentioned

Mendel, studied the urine, blood and other fluids, but while many of the facts ascertained were interesting, nothing of value was achieved; and, indeed, the subject did not assume even a scientific character until Bouchard introduced his theory and methods. Bouchard taught that the organism was a laboratory of poisons and this equally in the normal as in the pathological condition. In the normal condition these poisons are in one way or another made harmless, but in pathological states, when the protective measures of the organism are weakened, these poisons circulate in the blood and are excreted by the urine. Bouchard it will be remembered worked out a method of determining the degree of the toxicity of the urine, a method which found a later application also in the study of the toxicity of the serum. A definite amount of normal urine was found to be lethal to a certain weight of rabbit and thus was determined the coefficient of the toxicity of the urine. As the urine of the insane frequently showed an increase in this coefficient it was naturally ascribed to an increased output of poisons. However, the existing knowledge of physiological and chemical processes was not sufficiently advanced to render the results of value. No information was yielded as to the sources of the poisons and but little as to their character. Besides the method took no account of such an important factor as the difference between the osmotic pressure of the urine and that of the serum of the blood; and the findings were also confusing in that the coefficient sometimes rose with a maximal intensity of symptoms and sometimes rose with a minimal intensity, or instead of rising, falling under the same circumstances. These facts, while they admitted of explanation, did not do so in a satisfactory manner. Similar experiments were made and similar results achieved with blood serum, and in this connection Rebicci's observations that the blood of epilepsy, paresis, senile dementia and amentia is poisonous to the leech, are of historic interest, as are also other observations made as to the toxicity of the perspiration and of the cerebro-spinal fluid.

I well remember the profound interest which these theories of toxicity aroused, as likewise the disappointment which necessarily followed. We all of us remember, also, the extensive rôle that was at one time assigned to the uric acid group and its congeners, a rôle that to-day still demands consideration. The

leucomaines, as they were named by Gautier, are regarded, as is of course well known, as the products of the incomplete oxidation and hydration of proteid substances. In some respects they resemble the vegetable alkaloids, and it was at first believed that their presence in the urine was sufficient to account for the symptoms of a given case. All that it seemed necessary to do was to further the elimination of these poisons, or to prevent their formation, or in some way to render them harmless. These expectations were of course doomed to disappointment, but, though the doctrine of the leucomaines like the earlier views of toxicity failed of a definite result, the one great truth still remained, a truth which Bouchard and his followers had early perceived, namely the great fact of auto-intoxication.

The doctrine of auto-intoxication gained force from the subsequent and rapidly accumulated knowledge as to the rôle played by poisons of exogenous origin in the production of mental disease, notably alcohol and the infections. The disorders which these poisons cause,—delirium, confusion, stupor, dementia,—are now clearly recognized. Regis and later Kraepelin pointed out the rôle of the infections. Kraepelin was one of the first to insist that the mental symptoms are the result of the action of bacterial toxins. These toxins, it would appear, may act directly upon the cortex, or the infection may bring about disturbances in the functions of other organs, disturbances leading to changes in the general metabolism of the body, to the formation of endogenous toxins and to the consequent auto-intoxication of the entire organism. Infections variously involve the liver, the kidney, the thyroid, the adrenals and other glands and tissues. The fact of such involvement is based upon indisputable clinical and pathological evidence. That under such circumstances an intoxication may be very complicated and very persistent goes without saying. A proper appreciation of this fact lends renewed interest to the mental phenomena of infection. The prolonged confusions that now and then occur during the post-febrile periods of typhoid fever and other acute infections, the prolonged confusional insanity every now and then met with in alcoholic subjects, are clearly due not to the original infection, not to the poison originally ingested, but to the secondary toxemia of a deranged metabolism. Again, the part played by the in-

fections enables us to understand more clearly the mental phenomena every now and then observed in the early stages of the subacute infections, syphilis and tuberculosis. Here mental symptoms are often observed long before the physical signs peculiar to the infection become manifest, *i. e.*, long before organic changes occur. Such symptoms must necessarily be toxic in origin. That they occur early in paresis and early in tuberculosis every alienist knows.

With these considerations before us, let us turn our attention to auto-intoxication proper, that is, to primary or endogenous poisoning. A moment's reflection reveals that primary auto-intoxication is of two kinds; first, one that is gastro-intestinal in origin and another that arises in the tissues of the body itself. This distinction, however, may in practice be a very difficult one. An intoxication by way of the intestinal tract may give rise to secondary disturbances of metabolism within the body, *e. g.*, derangements of the liver or of the thyroid gland, or, intoxications having their origin within the body proper may be followed by a secondary intestinal intoxication; of this melancholia and other affections in which the innervation of the intestinal tract is diminished, afford abundant examples. In considering gastro-intestinal intoxication as a possible primary factor, we must bear in mind that in the normal or healthy individual, intestinal poisons are destroyed by the liver, the thyroid and by the other glands and tissues generally, or, eliminated by the various excretory organs. Poisoning of the nervous system is thus effectively guarded against. However, in diseased and defective states, it is possible that invasion occurs and that it may also produce, as above pointed out, secondary disturbances of metabolism. The presence of phenol, indol and skatol in large amount bespeak, of course, intestinal intoxication, but, on the whole, it may be safely said that when there are present marked or persistent nervous symptoms, we have to deal with a coëxistent and probably primary, interstitial or endogenous poisoning.

The detailed chemistry of the urine, a chemistry which deals largely with the end results of the disorders of metabolism, cannot long detain us here. The amount of nitrogen, sulphur and phosphorus excreted, the mineral waste and the output of water are all facts of great interest but are obviously secondary in im-

portance to other and more recondite changes. Suffice it to say that some of the facts suggest disturbances of the glands of internal secretion; others indicate relationships between different disorders, e. g. between migraine and epilepsy, between epilepsy and diabetes and between epilepsy and some forms of manic-depressive insanity.

However, the clinical histories and the course of many mental diseases suggest a more profitable line of inquiry. The facts suggest that we have to do with biochemical processes akin to those of infection and immunity. The history for instance of an attack of melancholia, its gradual invasion, maximum onset of symptoms, gradual subsidence and final recovery, is strangely like that of an infection. That we have to deal with fermentative or enzymotic processes is exceedingly probable. Let us see what the facts indicate.

Intoxications of short duration probably play here a relatively unimportant rôle; in brief intoxications we have to deal with poisonings which the organism successfully resists and, so to speak, disposes of speedily and promptly. For such resistance the organism is admirably equipped. We have in the very beginning the defensive action of the gastric and intestinal juices. If injurious substances notwithstanding gain access to the organism they are submitted to the action of that wonderful laboratory the liver and later to that of other glands and tissues. Substances are oxydized, deoxydized, hydrated, dehydrated or variously combined or disintegrated and finally eliminated. Such is probably the course of intoxications of short duration, but in those of long duration such as are commonly observed in mental disease, the organism doubtless has recourse to the formation of immune bodies; in other words, the organism reacts to intoxications just as it does to infection, namely by a defensive fermentation. The rôle that the fluids of the organism play in its protection we have been taught by Buechner, Bordet, Bouchard, Behring, Roux, Kitasato, Ehrlich and others. The agencies at work have been shown to be substances which bring about immunity by a biochemical action, an action that is probably reducible to physico-chemical terms. In combating the poisons which give rise to nervous and mental disorders, the phagocytes have, it would seem, no opportunity for the exercise of their

special function, but it is not improbable that they join the serum of the blood in furnishing protective substances. The truths revealed in the discovery by Behring and Roux in regard to the curative and preventive action of the serum of animals immunized to diphtheria, in the discovery by Kitasato and Behring of the kindred facts in regard to tetanus and by Simon Flexner in regard to cerebro-spinal meningitis, constitute stories of brilliant human achievement. Ehrlich's results in regard to ricin and abrin and Calmette's in regard to cobra poison are likewise familiar to us all. Nor need we call attention to the specific sera developed against definite microorganisms, the bacteriolytic sera, nor to the sera developed as defensive agents to erythrocytes, the hemolytic sera, nor to the numerous other cytolytic and cytotoxic sera that have been experimentally produced, such as the hepatotoxic, thyreotoxic, neurotoxic, spermatotoxic sera and others that might be mentioned. The doctrine of antigens and anti-bodies is destined it would appear to have an ever widening application. An antigen is, as we all know, a substance which when introduced into the organism is supposed to bring about the formation of a specific antibody. Among such substances are microorganisms, their toxins, cells of various kinds or extracts of their substance, poisonous and non-poisonous proteids and lipoid substances.

It would obviously be out of place to dwell here upon the details of the theory of the antigens and antibodies save to recall some of the basic facts, the application of which to our special inquiry will become apparent later. Thus, the body resulting from the union of the antigen and antibody is composed of two basic substances, one the thermostable, the other the thermolabile substance. The thermolabile substance can only combine with an antigen whether the latter be a microorganism, an erythrocyte, a toxin, a proteid or what not, after the latter has been prepared, *i. e.*, treated with a specific thermostable substance. The thermostable substance is the amboceptor of Ehrlich, the fixator of Metschnikoff, the corps sensibilatrice of Buechner and Bordet; the thermolabile substance is the complement of Ehrlich, the cytase of Metschnikoff, the alexin of Buechner and Bordet. It is significant that the thermolabile substance is found in the normal serum.

Let us now turn our attention briefly to the elementary facts

of precipitation, agglutination, opsonin reaction, and complement binding.

If a parenteral injection of an antigen be made into an animal, the serum acquires a new property, *i. e.*, when it is added to an emulsion of the material originally employed there ensues a flocculent precipitate. The antibody which is the cause of the precipitation, is in this instance termed the precipitin. Like other antibodies it has a specific character; that is, it causes a precipitate only with preparations containing the corresponding antigen.

The phenomena of agglutination are briefly summarized as follows: if the serum of an animal immunized to a bacterial culture or its products, be added to a liquid in which these bacteria are suspended, the latter begin to aggregate in masses and to sink to the bottom of the tube; of this the Widal reaction is a familiar instance. The antibodies are here termed agglutins and are of course specific in their action. Very little work has thus far been done upon the phenomena of agglutination in the sera of the insane.

Opsonins are, as is of course well known, substances which prepare microorganisms for consumption by the phagocytes. Opsonins exist preformed in the serum and are probably alexins or complements, *i. e.*, thermolabile substances. In how far they play a rôle in the defense in cases of mental disease of bacterial origin is of course an open question. The opsonic index is on the whole reduced in the chronic insane, though it is increased in some cases of dementia præcox and increased in the larger number of epileptics. It is interesting to know that D'Abundo found the bactericidal properties of the blood increased in paresis, in pellagrous insanity, in mania and melancholia, while in paranoia it was normal or not characteristic.

Complement binding—a reaction which was discovered by Bordet and Gengou—consists in the fact that when an antigen and its corresponding antibody meet, the complement is held fast. This fact can be demonstrated by the addition of a hemolytic system; if the complement has been held fast there is no hemolysis. This is of course the basis of the Wassermann reaction. However, the principle has been applied to the study of other affections than those supposed to be syphilitic. Thus Geiszler immunized rabbits with the serum of various cases of insanity by giving five or six injections into the abdominal region at in-



tervals of five or six days. After the third injection Geisler observed that the serum of the rabbits immunized with the serum of dementia præcox had acquired the property of complement binding with the serum of all dementia præcox cases, hebephrenics or catatonics, while the same serum yielded no reaction with the serum of healthy persons or that of patients suffering from other forms of mental disease. Similar results were obtained with the precipitin.

When we turn our attention to anaphylaxis, we find that it appears to be increased for tuberculosis in dementia præcox. This points to a connection in this affection between the functional disturbances of the glands of internal secretion and tuberculous infection, a fact to which I called attention several years ago.

The hemolytic action of the sera of the insane is alike interesting and important but cannot detain us here, suffice it to say that they show suggestive and significant departures from the normal in epilepsy, manic-depressive insanity, dementia præcox and alcoholism.

The lymphocytosis of the cerebrospinal fluid, so important as a diagnostic factor, depends upon changes foreign to those thus far considered and need not detain us farther than to point out that it is met with in paresis, tabes, cerebrospinal syphilis, the sclerosis, brain tumors, and in various forms of meningitis.

The rôle of antigens and antibodies, of precipitins and agglutins, the phenomena of complement binding, the play of the opsonins, hemolysins and other substances, suggest that all these processes are the expression of a common biochemical or physicochemical action, namely, of a fermentation. All of the processes of nutrition, all of the changes exhibited by proteids and carbohydrates, are the expression of such an action and occur under the influence of catalytic and enzymotic processes. Again the fact that ferments consist of two basic substances, first a zymogen and secondly an activator, goes far to prove the identity of fermentation and immunizing processes. Further, just as antigens lead to the formation of antibodies, so do ferments lead to the production of anti-ferments, *e. g.*, pepsin to antipepsin, trypsin to antitrypsin. Again, ferments also manifest the property of specificity; thus each ferment is active upon a specific substrate. Finally, in regard to fermentation in general, the conclusion is justified that it is a universal property of living matter. A point

of practical importance may be added, namely that many ferments preserve their activity for some time after the death of the organism; thus in a measure this subject is open to post-mortem study. The studies thus far made are intensely interesting; *e. g.*, it has been found that antitrypsin is increased in all cases in which the amount of proteolytic ferments is increased and in which a reduction of proteids with a corresponding degeneration of cell elements is taking place. Thus the antitryptic properties of the serum are increased in paresis during periods of increase of symptoms and diminished during remissions. It is interesting also to add that it is diminished after salvarsan administration. Similar phenomena of increase and decrease are noted in alcoholic insanities and on the whole the inference seems warranted that an increase in the antitryptic property of the serum is an unfavorable indication.

Let us now turn our attention briefly to the aspect of the subject of fermentation developed by Abderhalden. The method of study employed depends upon the fact that a foreign proteid substance introduced into the blood excites the production of a ferment, the action of which is to protect the organism against the foreign substance. Such a foreign substance may gain access to the blood from without or from organs and tissues within the body. An instance is the digestion of placental elements by ferments in the blood of the pregnant woman, the blood of the non-pregnant women and of men containing no such ferments. The work which Abderhalden and his pupils have done is already very large in amount and the subject has become so extensive as to be impossible of inclusion in so brief a statement as this address necessitates. Suffice it to say that Fauser and others have tested the digestive or reducing action of the sera of different forms of insanity in relation to the thyroid gland, the sex glands, the brain, the kidneys and other organs. Many remarkable observations have been made.

The time at my disposal will only permit of a few additional observations; these will be somewhat in the nature of general statements. First, proteids and lipoids alone can evoke the formation of antibodies, and in this process lipoids appear to play the rôle of activators, and their injection seems to bring about an increased formation of immune bodies. Second, the specificity of immunity and fermentation processes does not appear to be

entirely absolute. It is very probable that such biological conceptions as antigens and antibodies will be replaced, indeed, are being replaced, by more precise chemical conceptions. It appears that the curative action of a given serum depends upon its containing a larger amount of substances already normally present in the body. Syphilitic antigens, for instance, may be derived from various normal tissues but under the influence of the spirochete they increase in amount. Third, it is exceedingly probable that the physical structures of colloids is able to explain the processes of fermentation. Colloidal substances seem especially able to evoke the formation of antibodies. Fourth, in the struggle with intoxication and auto-intoxication, a most important rôle must be assigned to the glands of internal secretion. The various other tissues and organs of the body, in addition to their special functions, possess also the function of internal secretion inasmuch as they elaborate, as a result of their functional activity, and pass into the blood and other liquids of the body, certain substances which in one way or another act upon other organs and thus add to the number of the hormones as we now term them. The life of the organism is that of a well coördinated chemical whole. It is the disturbance of this coördinated chemical whole either by the introduction of foreign substances from without or by the breeding of foreign substances within the body through the breaking down of the coördination, that causes intoxication. Disturbances of metabolism, using this term in its widest sense, are therefore the basic factors in mental diseases, and this truth brings mental diseases properly within the province of internal medicine; but in order that they should be viewed in their proper perspective, the following important facts must be borne in mind. Mental diseases, as just indicated, separate themselves into two great groups; first one in which the disease is due to infection or exogenous poisoning and second one in which the disease is due to endogenous poisoning.

In regard to the first group, our therapeutics, our ability to interfere to the advantage of the patient, is in a far better position. In the second group, we have disorders which occur in organisms whose structure is chemically and physically essentially defective, deviate and aberrant. Their peculiarities are unfortunately hereditary and innate. These peculiarities do not manifest themselves markedly as a rule until the period of life is

reached at which metabolism assumes a special activity, that is, at puberty or later. At puberty, in adolescence, in early adult life, the sexual glands and with them all of the other glands of internal secretion and hormone producing structures and tissues, take on a new rôle, enter upon a new chemistry, and if the organism be badly constructed, be badly put together, this chemistry becomes aberrant and toxic, and mental disease results. How powerless we must necessarily be in the face of such facts need not be dwelt upon. However, two hopes are held out to us; first, in the manic-depressive group in which the entire picture is one of the predominance of antigens in the early stage—in an attack of melancholia or mania as the case may be—and of the predominance of antibodies in the later stage, it is by no means impossible that sera will be devised which will enable us to cut short such attacks and perhaps to practice preventive immunization for recurrences. It is with regard to the heboid-paranoid group, the great group of dementia præcox and paranoia, that the outlook is the most discouraging. Here we must necessarily be limited to simple physiological therapeutics, but even here if these procedures be properly applied much can in given instances be accomplished. It is, however, in the field of eugenics that the second hope arises, forlorn and distant as this may be. We physicians, however, know that defects of stock arise largely from the infections and poisonings from which the ancestors have suffered. Syphilis, tuberculosis, alcohol, are the potent causes of structural and chemical deviation and degeneration, much more potent than insufficient food or exposure. It is in the minimizing of these factors that the hope of the future lies.