Pathology of Mental Diseases—II*

Modern Aspects of Certain Problems

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MICRO-ORGANISMS AND TOXINS IN CONNECTION WITH MENTAL DISEASES.

THE evidence furnished by the morbid histology of the brain in the acute and recent psychoses is not in favor of anything approaching a virulent toxæmia, with the doubtful exception of the condition known as "acute delirium," or "acute delirious mania"; neither does clinical evidence point to such, with the same possible exception. The temperature-pulse-respiration chart in cases of acute and recent mental disorders shows very little evidence of febrile reaction. Toxins, if any, must be of a low degree of virulence. We know, however, that various drugs which are incapable of producing the bodily disturbance of reaction which accompanies an attack of one of the specific fevers, and from this point of view are not virulent, are nevertheless able to produce very definite mental disturbance. While morbid histology affords practically no evidence of acute toxæmia in the psychoses, the changes found are quite compatible with the operation of a toxin of a milder kind. This is true, apart from dementia paralytica, for acute delirium, acute mania or melancholia, the psychoses of exhaustion. Cases of the disorders grouped under the name "dementia præcox" do not, for all practical purposes, come to necropsy in the acute and recent phase, so that, unfortunately, we have no sufficient information in respect to these. The examination of the blood in the acute and recent psychoses with the usual aerobic methods, upon the usual culture media, gives negative results.

Of all mental disorders the condition known as "acute delirium," or "acute delirious mania," is that in which we should most expect to find evidence of bacterial origin, on account of the acuteness of all the mental symptoms and the existence of grave bodily illness. The rarity of this condition has largely prevented its proper study; among the rate supported insane, at any rate, it is extremely rare, and I can only remember to have seen two or three cases in my experience of twenty-four years, and one of these was at Bethlehem Royal Hospital, which does not receive the rate supported. No significance is to be attached upon scientific grounds to any organism hitherto found in the circulation in this disease. The condition is seen in connection with typhoid and other infectious disorders, and it would therefore appear that more than one toxic agent can produce it, unless, indeed, such acts merely as a predisposing cause. Kozowsky¹⁹ in a recent communication upon the pathology of acute delirium, states that staphylococci, diplococci, and the influenza bacillus have all been found in cases of that disorder, and this is not surprising, seeing that the state follows upon diseases in which these organisms are causal agents. I am not aware of any record of animal inoculations in connection with cases of acute delirium. The psychoses following upon specific fevers but rarely come to necropsy, so that we have no sufficient information as to the histological conditions present in the brain in such cases.

The Infection Psychoses.

This brings me to the consideration of the psychoses due to infection or intoxication processes. By these we mean disorders of mind, which amount to more than mere transitory delirium, and which supervene in the course of, or follow upon, infectious fevers, or specific diseases attended with fever. These psychoses seem to me peculiarly worthy of study, for thereby we are likely to obtain an insight into the pathogenesis of similar disorders of mind which arise without any obvious cause other than a mere deterioration of health. The infection psychoses, as they may for convenience be termed, are rarely seen in public institutions for the insane; in the first place, they are uncommon; in the second, they are mostly of brief duration. They are to be met with more frequently in the psychiatric clinics of university towns on the continent, no doubt because the patients are readily transferred thither from the ordinary medical clinics when they become troublesome.

Among the specific fevers, typhoid yielded up to recent years the largest number of these cases, but of late years influenza has been a potent factor. Friedländer gives 15 to 25 per cent as the number of cases of typhoid in which psychoses occur. Erysipelas affecting the head is probably the next most frequent cause; thereafter come malaria and pneumonia. Puerperal insanity, which belongs to the category of the infection

psychoses, is in a class by itself. These psychoses, while no doubt mainly appearing after the bodily illness has manifested itself, or at its close, may appear in the form of delirium or mania before there is any fever, and are then only ascribable to a toxin, and fairly comparable to a psychosis due to some drug, to a poisonous substance used in an industry, or to ptomaines. Furthermore, the mental disorder does not by any means necessarily go with high temperatures, even when it appears after the bodily illness has become definitely established. This is the first instructive lesson I draw from a study of the infection psychoses; they illustrate (in common with insanity from drug poisoning) the ability of a toxin to cause insanity. A second instructive fact is that there is no difference in the kind of symptoms by which one can distinguish the psychosis caused by one infection or intoxication from that caused by another. The brain reacts in common, limited, well-recognized ways, irrespective of the nature of the provocative disease, it reacts to toxins; from which it appears that different toxins are capable of producing the same effects upon the cerebral cortex.

These psychoses exemplify the most diverse clinical forms; thus, acute delirious mania, mania, melancholia, states resembling closely certain of those deemed characteristic of dementia præcox, others resembling those seen in insanity with epilepsy (e.g., states of agitation, post epileptic stupor), acute confusional conditions, an exalted state resembling that seen in dementia paralytica, the syndrome of Korsakow—with its preliminary agitation and subsequent disorder of memory and attention power; above all, they take the form of acute hallucinatory insanity. In the post febrile period dementia of varying degree is shown. In short, if we exclude systematized delusional insanity, the above summary includes practically all the forms in which disease of the mind manifests itself. The specific fevers can reproduce them all, so that differential diagnosis from like mental disorders as ordinarily seen is for the time being practically impossible. The only essential difference is that in the symptomatic psychosis the disorder is commonly of shorter duration than in the so-called "endogenous" psychoses, although after typhoid and influenza varying degrees of mental defect may last for years. The above considerations naturally prompt the inquiry as to whether the forms of insanity we are accustomed to meet with, of unknown origin, are due also to toxins, exogenous or endogenous. A third point which is noticeable in connection with the infection psychoses is that one and the same provocative disease (toxin) produces different forms of mental disorder in different persons, which is presumably due to individual peculiarities.

A special reference seems desirable to the pseudo general paralysis which occurs in connection with some of the specific fevers, a point alluded to by Bonhoeffer²⁰ in his study of the symptomatic psychoses. As far as I am aware the pupillary reflexes are never altered, but the typical mental symptoms are reproduced, and the speech is affected, although not typically, yet in such manner as to cause difficulty in diagnosis. The knee-jerks may be exaggerated. As the pupillary phenomena are not present in every case of true general paralysis it must have been practically impossible to diagnose the simulated from the real disease by the mere symptoms in days prior to the introduction of serological, chemical, and cytological tests in respect of the cerebro-spinal fluid. A further special reference may be made to the occurrence of symptoms indistinguishable from those given as characteristic of the katatonic variety of dementia præcox. There are the stupor, flexibilitas cerea, verbigeration, echolalia, and echopraxia, stereotypy, rhythmical movements, rigidity of attitude, grimacing, mimicking, tics, and negativism; in fact, there is the entire symptom complex of this type of dementia præcox. Bonhoeffer has recently given some good descriptions of this condition following upon typhoid and pneumonia. A condition resembling katatonic stupor has been described²¹ as developing in a case of pellagra; the patient apparently had a predisposition to mental disorder, as she had an attack of mania six years previously, before the pellagra showed itself. The infection psychoses furnish instances in which a given symptom complex is produced by more than one morbid agency, and therefore constitute an argument against

specificity in causation of the various kinds of insanity. The abnormal constitution of the brain in individuals falling victims to mental disorder would seem to be of more importance than the exciting cause; the *irritable* more important than the *irritants*.

The study of metabolism in mental disorders is in its infancy; methods hitherto employed are inadequate to deal with the subject. The same is true of chemical methods. The most concordant results are in respect to epilepsy with insanity, dementia paralytica, dementia præcox, and manic depressive insanity. But the changes observed up to the present are not pathognomonic.

That psychical disturbances influence metabolism is but another way of saying that the body is influenced by the mind. It having been demonstrated in a given case of insanity that a disorder of metabolism is present, the question of cause and effect remains to be determined. One of the best instances of parallelism between disorder of mind and disorder of metabolism, and one of the readiest to suggest itself, is the occurrence of glycosuria in conditions of mental agitation, or agitation with depression, such as occur in different kinds of insanity. According to Allers the periods of excitement of general paralytics and epileptics are associated with an excretion of acetone bodies. The origin of these is a matter of speculation. Then there is the phosphaturia connected with states of mental agitation. I fear that in such instances as these it is difficult to get beyond the unsatisfactory position of psychophysical parallelism.

Metabolism in Epilepsy.

The work of Rohde²² is cited by Allers as particularly exact and critical. He finds in severe cases a disturbance in nitrogen metabolism, there being a retention of nitrogen, which reaches its maximum immediately before the fit. The pre-paroxysmal stage is also marked by the appearance of an increased quantity of ether soluble acids. The significance of this expression is dubious, and it requires explanation. The retention of N would appear to be the characteristic of the fit-free stage, but it is not peculiar to epilepsy, for a similar condition has been described in connection with the katatonic phase of dementia præcox and in dementia paralytica. After the epileptic seizure there is an increased excretion of N, which reaches a maximum at the close of a series of fits, and after the *status* there is a negative balance. Uric and phosphoric acids are also excreted in increased amounts and also lactic acid; the last is probably due to muscular contractions and asphyxia. Guidi²³ from his researches into the pathogenesis of epilepsy, also describes a profound alteration in nitrogenous metabolism.

Metabolism in Dementia Paralytica.

The study of metabolism in this disease is rendered extremely laborious and uncertain owing to the restlessness of the patients and the difficulty of obtaining 24-hour specimens of the excreta. In 1908 Kauffmann²⁴ wrote a monograph embracing the study of a few cases, but the value of his laborious work is much diminished by reason of its unsystematic and diffuse nature. He brings out the point of the disturbance of the water balance; the balance is negative, the loss of water partly accounting for the enormous loss of weight in this disease. Other workers, as Allers refer to the great variations in the water balance. There are, further, great variations in weight not dependent upon food intake. The loss of weight is not counterbalanced by subcutaneous infusion of salt solution. The process of heat regulation is also disturbed. For the temporary febrile states which one observes in general paralytics, if the temperature is taken regularly every three or four hours, and for which there is no apparent cause, Kauffmann suggests, by way of explanation, the accumulation of intermediate products of metabolism. The fever thus produced brings about increased oxidation and so becomes extinguished. These febrile states have commonly been explained upon a theory of infection and not upon one of auto-intoxication. In dementia paralytica, and, in fact, in all psychoses leading to dementia, products of degeneration of nervous tissues (*abbau produkte*) are to be found in the glia cells, and cells of

* Kozowsky: Allgemeine Zeitschrift für Psychiatrie, Band lxxviii, Heft 4, 1911.

¹⁹ Bonhoeffer: Die Symptomatischen Psychosen, 1910.

²⁰ Cole: The Lancet, September 6th, 1913, p. 717.

²¹ Rohde: Deutsches Archiv für Klinische Medizin, Band xcv., 1908.

²² Guidi: Rivista Sperimentale di Freniatria, vol. xxxiv., 1908.

²³ Kauffmann: Beiträge zur Pathologie des Stoffwechsels bei der Psychosen, G. Fischer, 1908.

the adventitia of blood vessels, in considerable, sometimes in enormous, amount. These have commonly been looked upon as of a fatty nature, but on insufficient evidence. It remains to be seen what they really are from a chemical standpoint and, by experiment, what noxious influence they may have.

Recently Allers²⁵ has published the results of a prolonged research in the metabolism of dementia paralytica, his chief conclusions being that endogenous protein metabolism is increased, as evidenced by the negative nitrogen (and sulphur) balance, with uniform intake or nitrogen. Nevertheless, the metabolic changes are not carried out to their end stages; they are quantitatively greater but qualitatively deficient—incomplete. These definite metabolic changes, occurring at any rate in certain phases of the diseases, are regarded as showing the existence of a general, not merely a cerebro spinal, disorder. Before their significance for dementia paralytica can be estimated control experiments in other organic diseases of the nervous system are necessary, but these, as Allers points out, are as good as non-existent. It is highly significant that considerable metabolic disturbance may be present with but small loss in weight, for in persons prone to mental disorder slight losses in weight frequently go with a definite disturbance of the mental balance.

Metabolism in Dementia Præcox.

The katatonic form has been carefully investigated by Rosenfeld,²⁶ the four cases he worked with being in a stuporose state; they were upon a fixed diet and fed by tube. The positive result was that N was retained in considerable quantity in all cases, even in periods when insufficient food was taken and the body weight sank. The nitrogen he believed to be in the form of available free protein, and for reasons he states. Pighini²⁷ obtained a like result, but in the chronic phase of the disease (which is characterized by dementia, negativism, tics, and stereotypy), and phosphorus was also excreted in diminished quantity, while excretion of calcium and sulphur was increased. In the acute phase, or with exacerbations, characterized by motor restlessness, impulsiveness, and sensory excitement, the N balance was negative, and sulphur and phosphorus (especially neutral sulphur) were excreted in increased quantity, which Pighini ascribes to increased nucleo protein katabolism. In the final, chronic stage, characterized by dementia—instances of which so largely help to fill asylums—the chemical exchange is physiological, as one would expect. In the active phase of this disease, as in dementia paralytica, there are great variations in weight, not wholly dependent upon food intake; the latter may be abundant and absorption good, and yet the patient loses weight. The work of Rosenfeld goes to show that these variations, as in dementia paralytica, are due largely to disturbance in the water balance.

Grafe,²⁸ in 18 cases of stupor occurring in different forms of mental disorder—such as the katatonic form of dementia præcox, dementia paralytica—found a definite lowering of metabolism, especially in the dementia præcox cases. The production of heat was diminished to 39 per cent below normal. Apart from myxedema, such an extreme reduction is believed to be very rare. In these cases there was no marked emaciation and no hypotonicity of muscle. And such reduction is, according to Grafe, not found in chronic under nutrition. From the researches of Borstein, Bornstein and Oven, and Grafe it follows that the exchange of energy, as estimated in calories, is very considerably diminished, and below the limit of physiological variation, in some cases of dementia præcox.

Extremely little experimental work has been done in the metabolism of manic depressive insanity.

The Dyestuff Industry

ACCORDING to the daily press, the manufacturers of both cotton and woolen goods and other color-using industries in this country are being put to considerable difficulties in securing a sufficient supply of dyestuffs. One or more of these sensational articles stated that there was a possibility of this famine in dyes forcing textile mills to shut down and throw about 400,000 employees out of work. Aniline dyes are produced principally in the countries in which war now rages, and the chief source of the material used in the United States has been Germany. The interference with Germany in shipping dyes into this country at the outbreak

²⁵ Allers: Zeitschrift für die gesamte Neurologie und Psychiatrie, Band xvii., Hefte 1 and 2, 1913.

²⁶ Rosenfeld: Allgemeine Zeitschrift für Psychiatrie, Band lxiii., Hefte 3 and 4.

²⁷ Pighini: Rivista Sperimentale di Freniatria, vol. xxxii., 1906, and vol. xxxiii., 1907.

²⁸ Grafe: Deutsches Archiv für Klinische Medizin, vol. cii., Heft 15, 1911; Zeitschrift für Physiologische Chemie, vol. lxxv., Heft 21, 1910.

of the war immediately awakened serious apprehensions in the minds of some of those who had a knowledge of our dependence on Germany for coal-tar dyes.

The more recent articles on this subject published in the trade and scientific papers dealing with dyes, textiles and all industries depending in whole or in part upon German coal-tar products, refer to the situation as far less perplexing than the daily press originally seemed to indicate. In an article headed "Contributions of the Chemist to the Industrial Development of the United States—A Record of Achievement," by Bernard C. Hesse, *The Journal of Industrial and Engineering Chemistry*, April, 1915, raises the question: Is there a shortage? This question is not answered affirmatively, but Mr. Hesse goes on to show that the present difficulty, for instance, in the textile industry does not lie in the lack of dyes, but that the real cause goes deeper than the dyestuff question, because the mills cannot sell their goods. But, he says, if they could sell their goods in this country or elsewhere, they might buy more dyestuffs than they do.

Mr. William W. Skiddy of the Stamford Manufacturing Company, Stamford, Conn., according to the *New York Times* of April 11th, 1915, says:

"I think the excitement which has been caused by many of these articles is uncalled for, for the reason that there are dyestuffs in considerable quantities made in the United States. There are some who manufacture anilines in the United States, and there are also large manufacturers of vegetable dyes in this country, such as logwood, fustic, hyperic, etc. These dyes were made for a great many years prior to the knowledge of any aniline colors, and were universally used by the textile manufacturers and others who had to use colors."

About sixty years ago the United States manufactured practically all dyestuffs used in this country, but those colors were of vegetable origin. The dye-wood extract industry was developed here, but our methods were immediately copied by the Europeans, and many factories for making dyestuffs soon sprang up in England, France, Germany, Italy, and Russia, where labor was cheaper than in the United States, and the finished product could be imported for less than it could be made here. Another serious blow to the American dye industry was the rapid development of coal-tar dyes in Germany. Enormous quantities of these colors of almost unlimited varieties are now made in Europe and practically all of them have been introduced and are now in great demand among American color-using concerns. These are at present about 1,200 shades or combinations and they are still increasing.

It is gratifying to learn from various reliable sources that the domestic manufacturers by running full time can satisfy the normal requirements of the color-using concerns in this country. It is understood, of course, that American manufacturers cannot now make a number of the shades which have been recently produced in Germany, nor can it be determined what per cent of the color actually made available for use in this country will be of coal-tar origin. German dyestuffs will continue to come in and the position of the domestic manufacturer of coal-tar dyes may remain unchanged until the tariff laws are modified.

There is a fair possibility, however, that vegetable dyes are coming into their own again. It is claimed that the adjustment of the machinery in dyeing plants for the use of vegetable as against coal-tar dyes is not very great, as is shown by the fact that a number of textile manufacturers use both kinds of dyes, depending upon the material to be colored. Another factor in favor of the possible increased use of the vegetable dye is that the producers of this class of goods are fully equipped and can procure the raw material at the present time under the most favorable circumstances. The woods come chiefly from tropical America, and since the shipment of these woods to Europe is considerably curtailed, they are now offered in the American markets at figures below the normal.

While the use of dyestuffs in general has increased enormously in recent years, that obtained from dye-woods has decreased. From 1860 the quantity and value of dye-woods imported steadily increased until about 1880, when the coal-tar dyes began to come into general use. During the succeeding decades the amounts imported fell abruptly. The total value of dyestuffs (logs and extracts) used is given in the following table:

Year.	Value.	Year.	Value.
1860.....	\$838,186	1890.....	\$1,725,167
1870.....	1,337,093	1900.....	862,462
1880.....	1,808,730	1910.....	566,377

Since 1910, the annual imports of dye-woods amounted to about \$500,000. Among the woods used logwood stands first. It is of West Indian origin and is adapted particularly for coloring leather, and for dyeing textiles it is also considered by some as superior to all

artificial dyes. Fustic, which also comes from the West Indies, stands second in importance among the woods used for extracting a dye. It is used principally in dyeing woolen goods a bright yellow color. Young fustic, camwood, barwood, sanders, sappan, and the Brazils come into this country in varying quantities. In addition to these foreign woods, vast quantities of oak bark are used, as well as a long list of other vegetable tissue of minor importance. But this can hardly ever be satisfactory. Not only are most coal-tar dyes cheaper than vegetable dyes, but the variety of shade is far greater.

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