

## SOME RECENT WORK ON THE PATHOLOGY OF SCHIZOPHRENIA.\*

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INASMUCH as the following is a summary of results of investigations into the pathology of mental disorders that have been conducted at the Central Pathological Laboratory at the Maudsley Hospital during the past few years, I shall deal with the general results obtained by my co-workers in the broadest fashion, alluding only to such facts as appear to be relevant to the hypothesis I am putting before you. When the present investigations were begun we had already abundant evidence of anatomical lesions occurring in schizophrenia, worked out in this laboratory by Sir Frederick Mott (1), (2), (3), assisted by Mr. Geary. The completeness of this evidence is a matter of history and is not now seriously disputed. (A few of the slides from the collection left to the laboratory by Mott were here shown.)

The slides illustrating the nerve-cells of the cortex and the cerebellum, the testicle, the adrenal and the pituitary give evidence of a profound degenerative change.

We had, then, at the start, indisputable evidence of a generalized degenerative anatomical change in every tissue of the body, but apart from the very generally observed depression of the basal metabolism, there was no symptomatology which would accord with these lesions. The labours of Pighini (4) and others of the Italian school failed to discover any single fact in the metabolism that was directly characteristic of dementia præcox and allied psychoses. It seemed that the biochemical and neurological functions of the psychotic were very like those of the normal subject, except that there was a fairly general, but by no means universal, depression of activity. With these facts in mind we changed our methods of attack—we no longer looked for static differences between the psychotic and the normal, but concentrated on testing how a psychotic would behave when his organism was put to any stress.

One of the first pieces of evidence that the response to stimulation

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was abnormal in our patients was furnished by some simple experiments undertaken at my suggestion by Dr. I. M. Robertson (5), (6). It is well known that normally the ingestion of milk by a fasting subject is followed by a leucocytosis. In certain conditions of liver inadequacy the post-prandial leucocytosis is changed into a leucopenia, termed by Widal the "hæmoclastic crisis." The experiments on this food response were initiated primarily to test the functional activity of the liver in psychotics, though we were of course well aware of the occurrence of the hæmoclasia in various other conditions associated with a disturbance of the vegetative nervous system. For a period, nearly all the cases admitted to the Maudsley Hospital were examined—275 altogether—and on a subsequent clinical classification of the results by Dr. Petrie (7) it was found that the leucopenic reaction was obtained in 90% of twenty-five certain and probable cases of dementia præcox, and by five out of twelve doubtful cases. In another group of twenty-nine cases classified as anxiety neurosis, 76% gave the hæmoclasia reaction. One hundred normal subjects all responded with the normal reaction leucocytosis. A large number of observations by Capt. Mann (8), (9) and other workers made it appear very improbable that the response in the psychotic patients could be attributed to disturbance of the liver, and it was suggested to Dr. Robertson that she should make further experiments on the vascular responses to other simple stimuli. The evidence obtained pointed to the conclusion that the inversion of the leucocytic response to food ingestion in psychotics was a manifestation of an inverted vasomotor response. Further, it was found that the reactions to heat and cold, as evidenced by the blood-picture, showed an inversion in those cases that exhibited the hæmoclastic response. Again, the leucocytic blood-picture corresponding to changes of posture was similarly inverted. Now when an internally conditioned reversal of a reflex of the vegetative system takes place, the physiologist at once thinks of the possibility of a shift of the calcium-potassium equilibrium. Calcium increases the excitability of the sympathetic, potassium increases the excitability of the antagonistic para-sympathetic system, and by suitable adjustments of their ratios inversion of vegetative nervous reflexes may be effected. But the ratio of un-ionized calcium in the blood is a function of the acid-base equilibrium; thus we find ourselves led to study the possibility of some such acid-base shift having taken place in the psychotic organism. The valuable studies on the abnormal response of the blood-sugar curve of the psychotic to the stimulus of sugar ingestion, undertaken by Capt. Mann, pointed in the same direction (10). A valuable piece of evidence confirming this view

was obtained by Dr. Robertson by eliciting the leucocytic response to food in a number of normal subjects as soon as they were awakened in the morning. Under these conditions the normal leucocytic response was inverted to give the hæmoclastic reaction. Now, as we shall see, the sleeping organism is definitely shifted over to the acid side during the night, and these results made us feel strongly that we were pushing our investigations in the right direction. An investigation of the urinary reaction in cases of mental disorder, conducted by a team of workers, revealed in the majority of schizophrenic cases an acidity which indicated a disturbance of the acid-base equilibrium, with a displacement to the acid side (11), (12). The urinary responses of the psychotic were next examined, and it was found that the normal morning alkaline tide was absent in rather more than 50% of the cases of schizophrenia, and in the same proportion of patients classified as melancholia (13). In other words, these psychotics tended to remain during the day in the state of an acid shift which in the normal is established during the night and promptly reversed after waking. The normal alkaline tide following a meal was absent in 70% of the psychotic cases examined.

In the normal subject the reaction of the urine denotes the tendency of the organism to correct a shift of the acid-base equilibrium to the acid or alkaline side. The constant pH of the blood is ensured by two mechanisms—the renal and the respiratory. The kidney retains or rejects base, and the lungs increase or decrease the acid (carbon dioxide) output.

Now a series of observations on the renal response to the ingestion of acid and alkali convinced us that the renal mechanism for regulation of the acid-base equilibrium of the psychotic is intact. At the same time, the urinary acid gave us clear indications that the equilibrium was disturbed by a tendency to change over to the acid side, and all the observations made on the carbohydrate metabolism, the response to drugs, the vascular responses, fitted in with this view. The other mechanism for acid-base regulation—the respiratory mechanism—would thus appear to be unable to perform its task. Normally the tendency to an increase of acid ions is met by elimination of carbon dioxide and consequent lowering of the carbon dioxide pressure in the arterial blood, as evidenced by a fall of the carbon dioxide percentage of the alveolar air.

Thus a diet rich in acid valencies, such as meat, will cause excretion of an acid urine, and a low percentage of alveolar carbon dioxide. A vegetable diet rich in alkali will cause excretion of a urine tending to alkalinity and a high percentage of alveolar

carbon dioxide. To maintain these different carbon dioxide pressures in the alveolar blood, the ventilation will be increased in the first case and diminished in the second.

It now became our problem to investigate the activity of the respiratory centre, since a diminution of its exquisite sensibility to the carbon dioxide pressure of the blood would have the effect of diminishing the ventilation and hence increasing the carbon dioxide pressure. We found it very difficult to obtain, on the part of psychotic patients, the cooperation necessary for accurate estimation of alveolar air samples; the few cases observed, however, showed a high alveolar carbon dioxide pressure. A normal subject with the highly acid urine of the psychotic would of course have shown a lowered carbon dioxide tension corresponding with his increased ventilation.

Some preliminary difficulties had to be overcome in estimating the total ventilation of our patients. No arrangement that involved any perceptible increase of resistance to ventilation could be used, for the respiratory system is exceedingly sensitive to slight differences in pressure; for this reason, to collect large volumes of expiratory air in a bag or plethysmograph would utterly upset normal ventilation. Again, the psychological effect of a mask, or even a mouth tube, is to cause the patient to over-breathe. Eventually an electrically controlled automatic plethysmograph offering no appreciable resistance was devised, and the subject breathed through soft rubber nose-tubes which were so comfortable that we found it possible to forget their existence while wearing them.

The excitability of the respiratory centre was tested by administering 2% carbon dioxide whilst the patient was breathing into the plethysmograph and the volume of each respiration was being recorded on a smoked drum. The normal subject responds by an increase of ventilation. It was found that a number of cases of dementia præcox with a highly acid urine failed to respond to the carbon dioxide stimulus. Here, then, was an objective proof of the predicted depression of the excitability of the respiratory centre (14).

Dr. Marsh took our apparatus to Claybury Mental Hospital and examined a large number of cases from the admission wards (15). Taking together the groups of cases diagnosed as schizophrenia and melancholia, 88% showed a depression of excitability of the respiratory centre. Clinicians may at once raise the question of the association of the melancholic and the schizophrenic groups. I may state frankly that at this stage we are not prepared to deal with it. I suspect that, once we have established a definite pathology of mental disorders, we shall be inclined to classify our cases

by their bodily symptoms rather than by disorders of conduct. Be this as it may, we are at present content to examine all cases of insanity as they present themselves, and to leave the question of classification in pathological terms to a later date. So far we have dealt only with cases of schizophrenia and melancholia because they present certain general symptoms that indicate a depression of nervous activity; our work is very recent, and we must leave to a later date the consideration of manic disorders. One point, however, was established by Dr. Marsh: the depression of the excitability of the respiratory centre is not merely a symptom of a catatonic stupor. Some of his patients were restless and excited, and others might have passed for normal in their conduct without a close psychiatric examination.

Having established this almost universal prevalence of a diminished excitability of the respiratory centre to carbon dioxide we inquired into the excitability to an alkaline stimulus in our patients. In the normal, as we have said, the respiratory system attempts the regulation of the acid-base equilibrium, when threatened with a swing-over to the alkaline side, by heaping up carbon dioxide while the kidneys excrete alkali. As one would expect, the immediate response to the ingestion of 10 gm. of sodium bicarbonate was the diminution of ventilation and the excretion of bicarbonate in the urine. On testing a number of psychotics who had shown a diminished excitability to 2% carbon dioxide, we found that their immediate response was identical with that of normal subjects. We thus obtained the important evidence that the psychotic's respiratory system is not excitable to acid, but is so to alkali. The normal record shows, however, that after two hours the hypo-ventilation gives place to a hyper-ventilation. That is to say, the organism has got rid of the surplus alkali by the kidneys and now has an excess of the retained carbon dioxide, there is a shift-over to the acid side and the carbon dioxide is now blown off by increased ventilation. Now the psychotic's respiratory centre cannot respond thus to carbon dioxide: his kidneys function as well as those of the normal, but when he has got rid of all his bicarbonate there is no increased ventilation to enable him to blow off the superfluous carbon dioxide. We thus arrive at the paradoxical result that if we attempted to make a psychotic more alkaline with bicarbonate, we should ultimately render him more acid. The waking condition of the psychotic appears, therefore, to resemble closely that of the normal individual during sleep. During sleep we get an increase of the alveolar carbon dioxide and an acid urine, the increase of the alveolar carbon dioxide depending on a diminished excitability of the sleeping respiratory centre; a

change of mental activity in the direction of a retreat from reality accompanies both conditions.

Dr. Armstrong's work in our laboratory (*vide* p. 644) affords a further parallel. A prepotent factor in the buffering of the blood is the acceptance by the red corpuscles of the acid chlorine ion, thus setting sodium free to combine with excess of carbon dioxide in the plasma—the Hamburger phenomenon. In sleep the acid load of the corpuscles is increased, and Dr. Armstrong has demonstrated an abnormally heavy acid load on the corpuscles of psychotic patients during the waking period. Thus the kidneys and blood are doing their duty; it is only the nervous system that fails in the sluggish respiratory centre. But a still more curious fact has been brought to light by Dr. Armstrong. Normally during sleep, owing to the inactivity of the respiratory centre, the acid load on the corpuscles is increased; in the psychotic during sleep the already heavy load is lessened. The explanation is easy: during the day the normal man has to combat the tendency of the active muscles to pour into the blood carbon dioxide and some lactic acid; he does this successfully by his respiratory regulation. When night comes he is relieved of this acid inflow from the muscles, but, inasmuch as he is able to deal with it effectually by ventilation, there has never been any occasion for the corpuscles to take up an extra acid load, and it is only when he sleeps and ventilation is diminished that the corpuscles are called upon to relieve the effects of carbon dioxide retention. The psychotic ventilates no better during the day than at night; his respiratory nervous mechanism is always sleeping; hence, during the night at all events, he benefits from the absence of the acid products of muscular activity—the load on his corpuscles diminishes.

We thus arrive at a fact that may be of therapeutic importance: a normal man can withstand practically any normal acid or alkaline stress by virtue of his respiratory adjustment; the psychotic is at the mercy of his diet and his muscular activity. Man has acquired this faculty of respiratory regulation as an omnivorous animal, devouring now an alkaline, now an acid diet. Herbivorous animals like the rabbit resemble the psychotic; they cannot regulate except by the kidney; an acid diet of oats will reverse the reactions of their vegetative nervous system from those obtaining with a green alkaline diet.

We now come to the final consideration: What is the state of the nervous system that conditions these abnormal responses? We shall do well to hesitate before we postulate that, because we have a tendency to acid accumulation, the acid-base equilibrium of the tissues will necessarily be tending to the acid side. Many of

the facts, and particularly the results of bicarbonate ingestion, lead me to think that the converse proposition is the true one. The tissues may be over-buffered, *i.e.*, suffering from an excess of the sodium anion, and the retention of carbon dioxide represents an attempt to restore their equilibrium. On the other hand many facts are against this; the vasomotor responses seem to point to a shift-over to the acid side; the same may be said of the abnormalities of the carbohydrate metabolism and the inexcitability to insulin described by Mann (10). Incomplete oxidation in the nervous system would cause an acidification due to the formation of lactic acid, and the experiments conducted in our laboratory on the oxidation of thiosulphates tend to show a depression of at any rate some of the oxidation processes in the psychotic organism. To elucidate this problem will require much more work, and I prefer to suspend judgment.

The foregoing is a non-technical summary of our results; we may now pass to a brief consideration of their general bearing.

A discussion on ætiology in terms of psychogenesis and physiogenesis is merely an attempt to resolve an unreal problem which exists only as a product of confused thinking. It is a mental confusion that has constructed an unreal antithesis between the events occurring in the environment of the organism which lies within the body and the events occurring in the external environment. It springs from the cardinal error of an unreal abstraction of a static organism from its environment which substitutes a static image for the series of events in space-time that constitute the living self.

Our problem is a physiological one. We have seen that all symptoms so far considered may be regarded as indicating a depression of the functional activities of the organism as a whole. Is this depression a failure of the nervous system, due to disturbances of the acid-base equilibrium, to deal adequately with external and internal environmental stimuli? If so, whether the ultimate disease be curable or not, there is some hope of influencing the disordered conduct by appropriate biochemical therapy. The alternative is a common cause for both mental and biochemical symptoms in the shape of a generalized depression of nervous activity. If it were possible to remain purely scientific observers and to ignore the claims of therapeutics, it might be urged that the time is not yet ripe for such a discussion to be usefully pursued; but the urgent nature of the problem from the human side impels us to entertain—and possibly to act on—any not altogether unreasonable hypothesis. It may seem that the mechanism involved is far too simple. It might be asked whether it is possible that the integrity



of cortical function could depend on nothing more complex than a shift of acid-base equilibrium due to carbon dioxide retention. Such an objection can have no weight with the biochemist. So far from being a simple or gross disturbance, a shift in the acid-base equilibrium of a nerve-cell is followed by a chain of physico-chemical events of the utmost complexity, of which only a few links are as yet even imperfectly comprehended.

Even so, it may yet be asked whether such a disturbance of acid-base equilibrium occurs in conditions unassociated with mental symptoms. The answer to this question is that, as far as we know, there is no state parallel with normal mental conditions. The disturbances of acid-base equilibrium in cardiac, pulmonary, renal or metabolic disorders, such as diabetes, are of an entirely different nature, inasmuch as there is no depression of the excitability of the respiratory centre.

Is there any evidence that the acid-base disturbances can affect nervous function? I think we may say that there is. On the one hand, the effects of continued hyperpnœa are well known; it is possible after twenty minutes of voluntary over-breathing, which produces a condition of alkalosis by forced expiration of carbon dioxide, to cause a state of profound mental confusion often combined with hallucinations. On the other side the effects of carbon dioxide administration are sufficiently well known. But these confusional states are unlike those obtaining in schizophrenia. Clinicians are familiar with the dramatic remissions that may take place, during which it is sometimes possible to learn from the patient that during the period of catatonic stupor he has retained much of his critical faculties, and can give a connected account of all that has taken place. Indeed, we are sometimes driven to the conclusion that the benign stupor represents a retreat from an intolerable reality, and if such a view be correct, it might seem that more would be required than the respiratory shift of acid-base equilibrium to account for either the retreat or the sudden return. I am far from admitting that such cases are as simple as that, but it is in the power of every one of us to produce an analogous state. The behaviour of the sleeper is not precisely the behaviour of the dementia præcox patient, though if our sleep condition lasted years instead of hours it is by no means certain that secondary changes might not supervene which would diminish the difference.

Again there is abundant physiological evidence that the excitability of the cerebral cortex may be increased by an acid environment, though the converse proposition rests on less firm evidence. What will happen, then, if we bring our pathological findings to



a therapeutic test and attempt to stimulate our patients by altering the pH of their nervous system? If the inactivity of the respiratory centre depends upon an alkaline tissue pH, there are three ways by which this can be counteracted—we might increase the acid valencies of the diet, we might increase the carbon dioxide tension of the blood, or we might diminish the oxidative processes, thus setting free in the tissues acids which are difficult to oxidize. In 1914 Cuneo (16), an Italian observer, claimed that by diminishing or increasing the protein fraction of the diet he was able to produce either a calm or an excited phase in a schizophrenic patient. It is true that he was obsessed by an hypothesis that we now know to be mistaken, that is, that the ammonia production was the cause of manic excitability, but his results really tend to show that an increase of the acid valencies of the diet can heighten cerebral excitability. Loevenhart (17), more recently, tried to diminish the oxidative process in cases of catatonic stupor by injection of sodium cyanide, and as a result found that his patients became lively for a short period, during which the injection could be carried out; in another batch of patients he administered 15 to 30% carbon dioxide in oxygen, and claimed that he obtained complete remissions lasting from two to thirty minutes in cases of catatonic dementia præcox. A patient who had not spoken for six years became talkative and rational, and the others lost their catatonia and spoke rationally and with insight into their condition. Loevenhart's experiments are founded on his physiological investigations on tissue oxidation, of the cogency of which I am sceptical, but if the therapeutic experiments which, he claims, restored inaccessible patients to a more normal condition for short periods be accepted, they would tend to support the view that displacement of an acid-base equilibrium may be a factor in causing depression of mental activity. We are at present conducting experiments on the same lines by administration of acid ammonium phosphate with increased protein diet to some of the patients in the L.C.C. mental hospitals. It is as yet, however, far too early to make any definite statement. It is, of course, only in subjects with a primary depression of the respiratory centre that such treatment could be effective. The normal subject responds to acid or alkali therapy by controlling his carbon dioxide output, so that the acid-base equilibrium is undisturbed.

So far, then, as the possibility of stimulating the depressed nervous system is concerned, pathology seems to have indicated a possible line of therapy, but we cannot give any answer as to how far such stimulation might restore normal mentality in any particular case. In old-standing cases the presumption is that it would,

even if successful, only transform a quiet patient into a noisy one. If the anatomical findings mean anything, they mean that in long-standing cases a diffuse degenerative change has occurred throughout the body, and it would be as unreasonable to expect to restore the degenerated suprarenal, testicle or ovary, as to expect to establish a normal functioning cortex. In other cases, however, we observed spontaneous remissions accompanying such changes in the internal environment as are caused by acute infections with their acidotic tendencies, or perhaps by changes in the external environment which bring relief from social stress. Where such remissions occur, there may be a possibility of a biochemical therapy. At the best such treatment will be symptomatic till we obtain a fuller knowledge of the pathogenesis of schizophrenia, but, whatever may be our views on pathogenesis, it may fairly be urged that there are already within our knowledge some facts that help us to understand the bodily disorder that forms part of the disease.

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