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Part I.—Original Articles.

The Eighth Maudsley Lecture: Dealing with some of the Work done to elucidate the Pathology of Disease falling to be considered under the Rubric "Insanity." Delivered by EDWIN GOODALL, *C.B.E.*, M.D., B.S., F.R.C.P., Medical Superintendent, Cardiff City Mental Hospital; Lecturer on Mental Disorders, Welsh National School of Medicine; at the Quarterly General Meeting of the Royal Medico-Psychological Association, held on May 19, 1927, in the Great Hall of the British Medical Association House, Tavistock Square, London.

MORBID HISTOLOGY.

IT has not been given to many of those whom I have the privilege of addressing to watch the course of the scientific investigation of the pathology of the psychoses for a period of thirty-four years. Many of my hearers are scarcely old enough to feel the pangs of disappointment. It will be some twenty-five years ago that, in general, the attention of workers in the domain of the pathology of insanity began to slacken in respect of that aspect of the work which, till then, had mainly interested them, *viz.*, the morbid anatomy of the brain. The output of work in this field about then showed signs of diminishing. Attention began to be directed to the problem of pathological causation. Search began to be made for the pathological factors which expressed themselves in the morbid histological conditions found in the brain-cortex, and, passing on, if we note the interests of young graduates studying for a diploma in psychological medicine, we shall, I think, find that they are not in the direction of histo-pathology, but rather in that of, for example, the function of the endocrines, of the autonomic nervous system, possibly of bio-chemistry. My experience of published work from foreign clinics in psychiatry is that the same drift from histology is noticeable. Nevertheless, it would be unphilosophical

to take the view that research in morbid histology of the brain is not worth while, and a perusal of the literature shows the work in progress in the field of the normal histology of the nervous system. Improvements in technique—in the main due to German, Spanish and Italian workers (how comes it that this branch is so little cultivated by the British?)—will add to our knowledge, and thus research in morbid histology will be constantly stimulated.

The application of the method of photo-micrography in ultra-violet light to the study of the nervous system appears to date from about 1911. A series of studies in the human nervous system is reported by Weimann (1) (1925). This method may be of much significance in the study of the histology and histopathology of the nervous system, but the difficulties and sources of error associated with it will, however, prevent it from becoming a method of general use.

The origin and significance of the plasma-cells, found in dementia paralytica, encephalitis lethargica, and some other conditions; the functions of the different types of neuroglia cells, and of the microglia—these, for example, are matters of interest. A masterly contribution by Cajal (2) upon the topic of the neuroglia in general paralysis shows that the microglia was first fully demonstrated by means of the technique perfected by Del Rio Hortega. This work dates back only some seven or eight years, and it was led up to by the work of the Italian, German and Spanish schools.

Comparatively recent work has shown the neuroglia to be a more complicated structure than was thought twenty years ago. This development in normal requires to be further supplemented by research in morbid histology. The function and dysfunction of this structure are still mainly matters of hypothesis. A good account of the microglia was given by Del Rio Hortega in August, 1925 (3). This third element, as it has been called, of the nervous tissue is, in his view, not a part of the neuroglia at all, but a cell of mesodermic origin which has migrated into the nervous centres. From Hortega's description, based on histological and experimental evidence, one pictures the microglia cells as amœboid bodies, of varying figure, according as they require to adapt themselves to the local characteristics of the framework of nerve-cell, blood-vessel and neuroglia in which they have to function. The conception of function presented is that of a permeating tissue, subserving depuration in health, phagocytosis and scavenging in disease, these latter purposes being achieved by movement of the microglial elements to the site of disease. This was a conception formerly applied to the astrocytes, but never, I believe, on sufficient evidence.

As recently as December, 1926, the subject of the appearance and activity of the Hortega (microglial) cells in pathological states was dealt with at length by Creutzfeldt and Metz (4).

If we except dementia paralytica, senile and arterio-sclerotic dementias, the brain-changes found in cases of mental disease are uncharacteristic. As regards the so-called "dementia præcox" group, and especially the cases exhibiting catatonia and catalepsy, it cannot be admitted that morbid histological states described by individual workers as characteristic have been generally accepted as such—thus, that lesions of the ectodermal elements (which probably preponderate over those of the mesodermal tissue) are especially pronounced in the deeper layers of the cortex cerebri; that they are especially pronounced in certain cortical strata. The excessive fatty deposit found in ganglion cells of the cortex in quite young persons who were cases of dementia præcox is of note. This may be an instance of the phenomenon referred to by Leathes and Raper (5)—the conversion of fat normally present, which does not stain, into fat that does, because of a change in dispersion of the fat, leading to aggregation. The example they quote from Dudgeon is significant. Whereas normal heart-muscle of guinea-pig and other animals shows no sign of fat in the cells when treated appropriately with Scharlach R., these cells similarly treated 24 hours after the injection of diphtheria toxin "may be densely studded with deeply-stained droplets and granules. Chemical analysis shows, however, that the normal heart may contain as much fat as the deeply-stained poisoned cells, or even more, though none of it is revealed by the staining." It is notorious that great difficulty surrounds the proper investigation of these cases of malignant dementia of adolescence ("dementia præcox"), since they succumb comparatively late in the course of the disease, and from intercurrent maladies. The histopathological conditions present at the base of the brain (basal ganglia, third ventricle environment, and mesencephalon) would be of great interest. Schuster (6) made a contribution in 1926 upon the patho-histology of two cases of dementia præcox which showed during life striking psycho-motor disturbances, in which muscle-rigor was present up to the end of life; severe ganglion-cell degeneration and neuronophagy were found in the vegetative centres and basal ganglia and nuclei which are brought into association with the psychomotor disturbances.

Although it is probably the prevailing opinion at present that the motor disturbances seen in catatonia are not due to pathological processes in the sub-cortical areas, but to such in the grey matter of other regions of the encephalon (degeneration of the nervous

parenchyma), recent work tends to give us pause; more work is needed upon this important point. Apart from the instance cited above, pathological changes have been described in the extra-pyramidal centres in cases diagnosed as dementia præcox, affecting both cells and blood-vessels (7). In order justly to appraise such work we require particulars regarding the clinical symptoms and signs exhibited by the patients, their ages, accompanying bodily disease, if any, the cause of death, and the pathological conditions found *post-mortem*. In so far as material has been available from cases free from intercurrent (especially infectious) disease, at the disposal of competent workers, and within a few hours of death—a rare combination—the histo-pathological data point to changes in the encephalon, not inflammatory, but degenerative, and of a widespread nature. Cerebrum, cerebellum, mesencephalon, pons and medulla, basal ganglia and extra-pyramidal structures—lesions have been described in all. More evidence is required before statements made concerning a concentration of these lesions in the subcortical areas in cases of the catatonic type can be accepted (8). As regards what may be described as the malignant psychoses of adolescence and early manhood, it would be more scientific if the superficial evidence of defective development, which so many of these cases yield, were confirmed by systematic examination for stigmata of degeneration. For these, and other instances of the psychoses, such examination, after a scheme sufficiently comprehensive, is desirable.

Corroborative evidence of infantilism, of Mott's observation on arrest of spermatogenesis and regressive atrophy of the testes, and on the decay of nuclei of the cortical nerve-cells, is required. Witte (9), giving careful regard to the various sources of error (due to secondary disturbances), considers that in about 60% of cases of schizophrenia (controlled by other cases) the testes are abnormally small, and very often there is defect or absence of spermatogenesis. These conditions he regards as the expression of inborn deficiency of the testes. The diminution of the interstitial cells, which Mott described, is, according to this writer, but rarely found. The views of Mott are in general corroborated by Münzer (10) in a particularly valuable contribution on an individual case. If it is hereafter established that the testis (and the ovary) presents morbid histological conditions in some kinds of adolescent dementia, it will be reasonable to expect research with a view to ascertaining whether any reactive substance can be discovered in the blood-serum.

The hopes raised by the Abderhalden procedure for the demonstration of specific antibodies in the blood-serum extended to the domain of psychiatry, so that about 1913 a considerable amount of

work was done in Germany in that domain with this method. It could not, however, be decisively demonstrated that breakdown-products of protein of genital gland, cortex cerebri, or any other tissue were present in the circulation, and gave rise to protective antibodies. After a brief experience of the Abderhalden procedure, as originally described, I, in common, I believe, with most who tried it, concluded that the complicated technique and sources of error therewith associated ruled it out as a practical method.

It seemed as though the Abderhalden method had been discarded, but evidently much patient work has been bestowed upon it since the above date, as reports are again appearing, at any rate in the German medical press, upon clinical work carried out with improved technique, whether with the dialysing method, or by the methods of interferometry and refractometry.

The results obtained with these methods are not encouraging. In July, 1926, Kafka (11), of Hamburg, than whom there is no more experienced worker in serology, described his experiences with new methods worked out by Sellheim, Lüttge and v. Mertz, which dispensed with dialysing. In substance, these consist in obtaining the dried organ-powder (of the tissue to be tested) by a technique described, adding to this the serum to be tested, incubating, and further adding aldehyde-free 96% alcohol, and, after boiling and filtering, adding the ninhydrin solution used for the test. A control tube of serum without organ-substratum is put up. A definite blue reaction is positive. Kafka's results go to show a preponderance of strong reactions with gonadal tissue in schizophrenia—mostly associated with reactions with brain-cortex and thyroid; a remarkably constant reaction with thyroid in epilepsy; preponderatingly negative results in manic-depressive psychoses with the substances giving positive results in schizophrenia. This interesting communication should incite to further work on these lines.

To pursue for the moment the subject of antibodies or ferments: The diastase-content of the urine is an index to the amount of diastase in the blood. Scholberg and I (12) examined the urine at least twice, and in many cases oftener, in 120 instances of mental disorder of various kinds, as admitted into a public institution, and found a normal diastase value in all except 7 cases. Evidence of kidney disease was absent in these 120 cases with one exception. In view of recent work by von Strasser (13) upon the diastatic ferment in blood, embracing patients suffering from many forms of disease as well as healthy persons, it seems clear that normal diastase-values in the serum are only found to be exceeded where there is good reason to suspect that the pancreas is involved (especially in pancreatitis).

As regards proteolytic and so-called lipolytic ferments in blood, it is the case that some work as regards the former has been published in respect of epileptics, but I am of opinion that in the present state of knowledge we are not in a position to study the action of these ferments in cases of disease.

While one must recognize that it is very difficult to obtain pathological material from typical cases of the psychoses sufficiently free from the complicating effect of intercurrent disease to render it of value, I, nevertheless, think that we have not taken, and are not taking, sufficient advantage of our opportunities to study the morbid histology of the glands of internal secretion in cases of adolescent dementia—a subject on which we are very badly informed. Its importance was recognized, I would recall, by Sir Frederick Mott, whose pioneer work on certain of the glands of internal secretion we are familiar with. The study of as many as possible of these glands in one suitable case is more likely to be informative than that of an individual gland in many cases.

At this point, a few words as regards remissions in dementia præcox. Since these occur, transforming the clinical picture in many cases dramatically, producing such a degree of amelioration that the patient is fit for discharge, mentally well for the time being, and even able to take up a subordinate occupation, it becomes a duty, and an interesting one, to seek out Nature's method of bringing about the change. Many of us who had charge of mental cases amongst troops during the war must have been struck by what appeared to be recoveries in cases which, in ordinary civil experience, would have been classed as dementia præcox. These cases could not be followed up, and may have been instances, some of wrong diagnosis, others of dementia præcox in remission. These remissions in dementia præcox are doubtless less frequent and less complete than those noted in dementia paralytica. In neither case do we know to what they are due. While they can be imitated—probably improved upon—by the malarial treatment in dementia paralytica, I have not been able to find evidence that any success has attended this or the like empirical means when applied to the case of dementia præcox. There is a fascinating field of work which may be commended to the juniors in our branch of medicine in respect of the phenomenon of remission in both the diseases mentioned. The conception—and it is no more, and one based on observations in need of extensive corroboration—of a premature decay invitality in cases which break down at adolescence, is likely to damp the ardour of the research worker, and to exalt the horn of the numerous pessimists who, unemployed, frequent the glades of psychiatry. The evidence of remission should act as a corrective

and a stimulant. Indeed, I would suggest that the clearing up of mental and physical symptoms and signs sometimes seen in dementia præcox is difficult to reconcile with a doctrine of premature decay of neurones and endocrinal tissues, and justifies the working hypothesis that, in order to have a remission, an exciting cause must be put out of action. Most people will work only in faith, and if this form, like others, has its detractors, it will inevitably have its devotees likewise. We must, I consider, look to the neuro-psychiatric clinic in all countries to deal with the problem of the pathogenesis of the dementia of adolescence—in my view, far the most serious and the most difficult of the problems of psychiatry. Such a clinic, because of its superior staffing and research facilities, and because these cases will be seen in earlier stages than at the present mental hospitals, will be in a far better position to conduct this investigation than are the latter.

If this be sound, then how do we stand in this country, with its primitive organization for dealing with the problems of psychiatry?

Bonhoeffer, who deals with the psychoses associated with infectious diseases in Aschaffenburg's authoritative *Handbook of Psychiatry*, points out the great difficulty—indeed, sometimes the impossibility—of diagnosing between catatonia in its acutest phases and a similar condition seen in the infection-psychoses. He states that there is no single catatonic symptom that may not be found in the latter. Diagnosis, if feasible, must be made by the help of certain accompanying symptoms, and from the history. A similar difficulty has been described in respect of cases of poisoning by CO (14). I doubt whether sufficient attention has been bestowed upon this clue.

Toxæmia.

In the Presidential Address which I had the honour to deliver before this Society in 1923, I summarized the work which, to the best of my knowledge, had been done in the domain of bacteriology in the acute and recent psychoses. I am old enough to remember the introduction of bacteriological methods into mental hospital laboratories, at approximately the date when histological research had reached its apogee. In this direction, also, interest has waned, so that for some fifteen years little or nothing has been published. My summary of bacteriological investigations, including personal investigations in association with colleagues, dealt with the examination of the blood, urine, fæces and cerebro-spinal fluid. The results have not thrown light on the essential pathological causation of the psychoses. But improvement in mental disorders has been recorded as following upon removal of

sources of infection in the mucous tracts. As regards our knowledge of the intestinal tract as a source of infection, I consider that the position is still very unsatisfactory. For a few years prior to 1914 my colleagues and I at the Cardiff Mental Hospital Laboratory had carried out much tedious work on the bacteriology of the fæces in states of acute melancholia and mania. An extensive survey in 1914 of all the foreign literature of importance enabled me to state that extremely little work had been done in this direction. Knowing as we do the striking effect upon the mental state of dealing drastically with the extreme constipation present in numbers of newly admitted patients, and appreciating the evidence of radiograms after a barium meal in these cases, it is clear that some toxic agency or agencies are at work, as to the nature of which, in my opinion, we are wholly ignorant. In the work on the bacteriology of fæces in acute mental disorders just alluded to we were unable to confirm the statement that had been made by the Italian observer, Pardo, that the putrefactive anaerobes of the intestine were increased. According to quite recent work of Kaemmerer and others, of the Medical Clinic in Munich, porphyrin has significance as a criterion of intestinal putrefaction. In its formation the obligatory anaerobes are the chief factors. We therefore carried out tests with the technique of Kaemmerer in 12 cases of acute and recent mental disorder, but in none could porphyrin be found spectroscopically.

As Bergeim (15) says, more satisfactory chemical indices of intestinal putrefaction are much needed. He has employed as such an index the reduction in the intestine of ingested ferric oxide, using the rat for the experiments. It was found that the oxide was reduced almost entirely in the cæcum and large intestine; that a carbohydrate diet, which altered the intestinal flora to an aciduric type, resulted in marked diminution of intestinal reduction; that intestinal stasis led to marked increase in reduction. This line of work seems worthy of further study, with a view to ascertaining whether the reduction is actually to be ascribed to the preponderance in the large bowel of the bacteria which produce proteolysis and putrefaction (usually described as, mainly, obligatory anaerobes). Is the reduction an index to such preponderance? If so, do toxic states result from such? In German literature one comes across references to the effects of absorption of "Darmfäulnis produkte." These putrefactive products arise from proteolysis in the bowel, such bodies as indol, phenol and kresol resulting. The estimation of indican and phenol in the blood in difficult. Notwithstanding all the work done on the former, I do not believe exactitude and reliability of method can be claimed. Becher and others (16) have recently described a colorimetric method for phenol,

which they claim estimates that substance, free and bound, in blood, etc., "with sufficient exactitude." The presence in excess of such substances in the blood is clearly bound up with the factors of diet and of kidney-function, whatever other morbid factors may be involved. I hope to refer to the importance of routine functional tests on our patients.

Ford Robertson and Cotton have drawn attention to the foci of infection which exist in the gastro-intestinal tract in the insanities, and in quite recent times Mazzanti (17) reported upon 12 cases of confusional insanity which came to *post-mortem*, of which 8 showed macroscopic lesions of the intestine; three of them, studied histologically, macroscopic lesions likewise, of the intestinal wall—intense congestion, hæmorrhage and degenerative changes. These acute alterations permit, according to the author named, of abnormal absorption of toxic substances from the intestine. In these cases the small intestine especially showed the lesions. How often is the small intestine cut open and examined at mental hospital autopsies? In my belief this is but seldom done. One of my colleagues and I, with the skilled assistance of Dr. Robert Knox, of King's College Hospital, studied the passage of a barium meal in 34 cases of mental disorder (18). Stasis, ptosis, and spasticity were marked. Dr. Chalmers Watson, of Edinburgh, described much the same findings. These results were recorded in 1922 and 1924, yet I have seen but little record of further work, obviously necessary, in this direction.

Henry (19), who has also studied this subject, remarks that such study shows evidence of relationship between psychoses and altered function of the vegetative nervous system, with which I agree.

These radiograms furnish an argument for the systematic employment of colonic lavage in newly-received cases of the symptomatic psychoses—to be continued as long as bed-treatment is maintained. It is not easy, though desirable, to make fractional tests of the duodenal contents in acute and recent cases of insanity. It has been shown in other forms of disease that, under the abnormal conditions obtaining, organisms which normally have their habitat in the large bowel migrate upwards, and are found in the small gut, including the duodenum. Substances secreted by the intestinal mucosa, which normally destroy bacteria or inhibit their growth, are deficient or absent. This point, of the prohibitive difficulty of carrying out tests and treatment of very many of the insane, which are more or less routine in ordinary disease, is, I think, scarcely allowed for by our colleagues in general medicine, who criticize the paucity of our research output. Take such an investigation as an examination of the N-partition in blood, cerebro-spinal

fluid and urine in typical forms of mental disease: the very cases we desire to investigate, and at the earliest possible moment, elude us, by reason of restlessness, resistance and faulty habits.

In the Croonian Lectures of 1913, before the Royal College of Physicians, I dealt pretty fully with the work, including my personal work, done upon the leucocytal count in the psychoses. I think we are entitled to conclude that the leucocytosis, with polynucleosis, found in many of our acute and recent cases points to toxæmia, albeit not severe. The evidence of a mild acidosis furnished by the CO_2 combining power test points in the same direction, as does also the evidence of nitrogen-retention. With these two points I deal later. These indications of toxæmia support clinical evidence of the same—a mild toxæmia, therefore, not bacterial, but of unknown origin.

The psychoses due to exogenous toxic or infectious processes constitute a welcome link with general medicine, and seem particularly worthy of study, as tending to afford an insight into the pathogenesis of like mental disorders arising without obvious cause. Such conditions as typhoid, malaria, influenza, pneumonia can produce all forms of insanity, or very good imitations of it, except a systematized delusional state.

Bonhoeffer, in his well-known study of the symptomatic psychoses, deals with the pseudo-general paralysis which occurs in connection with some of the specific fevers.

The complete symptom-complex of the catatonic variety of so-called " dementia præcox " has been described as following upon typhoid and pneumonia. A pseudo-general paralysis occurs as a result of toxæmia of intestinal origin in persons with neurotic inheritance. Such a case at the Cardiff City Mental Hospital was described by one of my colleagues (20) in 1924. In this there was mental confusion, exaggeration of the deep reflexes, unsteadiness of gait, defective speech (to test-words), loss of pupillary reaction, direct and consensual. A radiological examination revealed marked atony of the stomach, with proptosis, delay at the ileo-cæcal junction, extreme stasis, with spasticity, of the colon. Some three weeks' treatment was necessary to overcome the marked constipation present. The patient recovered in two and a half months, and was under observation at the Out-Patients' Psychiatric Clinic for over a year, during which time she remained well; she has not been seen since.

The question of toxicity of the body-fluids of persons suffering from the various kinds of insanity has not been thoroughly inquired into—a surprising state of things (21). The literature contains merely isolated and desultory references to the subject. In such work as has been done the animals used have been rodents in

practically all cases. In a systematic investigation animals higher in the scale should be employed. Probably the work done by my colleagues and myself—in which rabbits and fowls were used—is the most extensive as regards the psychoses, material, in the shape of serum, red blood-corpuscles, stroma of such, and cerebro-spinal fluid, from all the main clinical varieties of insanity being employed. The number of rodents and birds employed was very large. Control material was obtained from healthy farm-patients of a chronic class. The net result of these observations was that the deaths and losses of weight noted in the creatures injected with serum and red blood-corpuscles from cases of the psychoses (cerebro-spinal fluid produced no deaths) were not greater than those observed in creatures injected from control cases. For some unknown reason the stroma of corpuscles from cases of grave mental disease produced a heavy death- and loss-of-weight-rate, which was entirely absent when stroma from the controls was used. But in this particular case more numerous controls are desirable. In our experiments the rodents and birds were injected intravenously, in some cases intraperitoneally. Subdural and intraperitoneal injections are desirable.

One of the most interesting statements that I have come across is by Loewe (22). He found that the dried insoluble adialysate of urine from the catatonic type of dementia præcox, from dementia paralytica (after seizures) and from *delirium tremens* was highly toxic. From cases of epilepsy this is, in addition, capable of producing seizures very like epileptic ones, when injected intravenously. Similar adialysate from the urine of normal persons was not toxic. As regards toxicity of fluids (serum, urine) of epileptics or general paralytics, it is the case that statements in a positive sense have been made as to fluids withdrawn shortly after seizures, but findings in the pre-paroxysmal state would be of more importance.

In keeping with this evidence of lack of toxicity of the blood and cerebro-spinal fluid in cases of the psychoses is the result of a large number of experiments carried out by my colleagues and myself, which showed that there is no specific antisubstance (precipitin, hæmolysin, hæmagglutinin) formed when serum, red-blood corpuscles and stroma of such is injected into rabbits intravenously, even from recently received cases of acute mental disorder. As regards cerebro-spinal fluid from cases of general paralysis, this failed to produce any antibody in the serum of rabbits.

Metabolism: Some Observations.

About 1913, Allers, of the Munich Psychiatric Clinic, published a critical survey of the information then available in respect of

metabolism in the insanities. The subject had been worked at then for some nine years, but most of the work gave evidence of lack of training and inadequacy of method. A notable exception was the work of Folin and Shaffer (23), entitled "Some Metabolism Studies, with Special Reference to Mental Disorders." This classical and exhaustive study led to the following conclusions: A strong suggestion that general paralysis is a disease which may be associated at one stage or another with some metabolism disorder. Among other classes of the insane, pronounced variations (abnormalities of metabolism) from normal standard values are also very numerous, but no one metabolism-peculiarity could be identified with any particular form of mental disorder. The necessity for devising accurate analytical methods before this work could proceed is dwelt upon by Folin. His work was carried out between 1900 and 1904, since when chemists have been engaged in elaborating accurate methods for the examination of the chief constituents of urine, of blood-plasma or serum, and of cerebro-spinal fluid; in regard to the last two fluids, methods being adapted to the small quantities of fluid usually available, or the minute quantity of the constituents to be examined in the fluid. Thus, at our Chemical Laboratory at Cardiff, much patient research has been required in order to work out accurate methods for the estimation of reducing substances in the plasma and cerebro-spinal fluid, the components of non-protein nitrogen in the latter, and phosphorus and calcium in both fluids. As far as my knowledge goes, apart from the work of Folin upon urine, nothing of importance has been published in regard to metabolism in the psychoses except a small amount of work on basal metabolism, more particularly in states of stupor and in the insanity of adolescence. In this, as in other lines of research upon cases of mental disorder, including the early phases which it is so very desirable should be investigated, we are hampered by, to say the least, the lack of co-operation of our patients. Basal metabolism—or the energy output required to sustain the essential vital processes—has been occasionally estimated in mental cases of a limited class, as far as my reading goes, since 1908. Thus, Bornstein (1908–10) investigated 12 cases of the hebephrenic type of dementia præcox by the Zuntz-Geppert method (analysis of samples of expired air), and in the majority found a marked diminution in oxidation. Grafe (1910–11), in 18 cases of stupor occurring in different forms of mental disorder, also found a definite lowering of metabolism, especially in the dementia præcox cases, 39 being the figure given. For some time prior to 1923, my colleague, Dr. Walker (24), carried out painstaking research upon the basal metabolism in mental disorder, especially dementia præcox. In this

condition there is evidence of lowering of function, such as a subnormal temperature, cyanosed and cold extremities, damp hands, bradycardia—symptoms referable to a disturbance in function of the vegetative nervous system. Cases brought to me at the Out-Patient Department in Psychiatry, Cardiff Royal Infirmary, quite often show like symptoms. They should be warded in an indoor clinic, and have their basal metabolism investigated, among other functional tests, as a routine procedure. Dr. Walker, in his research, employed the Douglas bag method of indirect calorimetry, with a specially-made face-mask, the usual mouthpiece being unsuitable for mental cases. Haldane's apparatus was used for analysis of the expired air. Forty-four cases of mental disorder had 200 estimations made upon them. Thirty were cases of dementia præcox (without evidence of hypothyroidism). Of these latter cases, 50% had a basal metabolism of less than 10%—the range being from 12% to 47%—with 20% as the average. The non-dementia præcox types had either a normal basal metabolism, or one slightly in excess of this. In cases observed in a state of remission, the symptoms known as " vagotonic "—to which I have alluded above—disappeared, and a rise took place towards a normal rate of metabolism. Bowman and Fry (25) show in a table of all the cases of dementia præcox (schizophrenia)—125 (including Walker's)—which they could at that date (close of 1925) collect, the tendency towards a low basal metabolism (not necessarily below a normal limit of 10%), which has been noted by all observers. These authors noted the same tendency in instances of psychopathic personality, and—though less marked—in the depressed phase of manic-depressive insanity.

In connection with this subject I refer to diathermy as a means of treatment. This has been employed by us for many years. This treatment raises the pulse-rate and the body-temperature, increases the elimination of urea- and ammonia-nitrogen, and—as shown by Walker—increases the basal metabolic rate 10–15%. It is, therefore, indicated in the class of case above referred to. Now that artificial sunlight treatment is being introduced in psychopathic institutions, its effect upon basal metabolism in suitable cases should be recorded. Indeed, I consider it incumbent on those who have the installation for this treatment to furnish scientific evidence for or against the utility of the treatment in psychopathic cases—evidence based upon tests of function, blood-examination, etc. It will be time enough for mental hospitals in general to make provision when such evidence is forthcoming. Recently my colleagues and I have made systematic use, in suitable cases, of the method of the estimation of oxygen-consumption, in

order to get information upon the basal metabolism, using the British Benedict apparatus. It is affirmed by competent observers that with this method, applied with the necessary precautions, reliable information for clinical purposes can be obtained in regard to whether the general metabolism is raised or lowered. In the course of my reading I have found repeated confirmation of this statement. It is stated (Bernhardt (26)) that, by this method, the basal metabolism can be estimated with no more error than 1–2% in patients who have been duly trained. Lusk (27), experimenting with the dog, and Atwater and Benedict with man, find that the percentage difference in the calories produced in the same period, as estimated by indirect calorimetry (analysis of the respiratory gases) and direct calorimetry, is no more than 0·6 and 0·2 respectively.

A modification has been employed in the British Benedict apparatus used by us, in the interests of accuracy, in accordance with a principle introduced, according to my reading of the literature, by Knipping (I believe, of Hamburg). Valves are dispensed with. A small motor pump is interposed between the O_2 cylinder and the patient, and adjusted to run at a speed calculated to bring about the movement of gases of respiration so that the patient breathes at a normal speed, thus relieved of any effort (involving expenditure of energy), such as, with the ordinary apparatus, is necessitated by such causes as valvular resistance, friction of walls of the rubber tubing, stagnant gas or products of respiration. Repeated observations with this modified apparatus give results which accord well.

My thanks are due to Dr. R. V. Stanford, of our Chemical Laboratory, for valuable technical assistance and general advice in regard to the modification mentioned.

The metabolism of suitable patients might be further studied by recording the so-called specific dynamic effect of food-stuff after ascertaining the basal metabolism. This is done by giving a mixed test-meal of beef, carbohydrate and fat, which is known normally to raise the consumption of oxygen by a certain percentage, which is at its maximum in, say, 1½–2 hours, and observing the actual effect upon the consumption of oxygen; or these constituents are given separately (*e.g.*, roast meat 200 grm., glucose 100 grm., fat 100 grm.). With adequate staff, further tests could be done, such as tests designed to show the utilization and elimination of water, sodium chloride, glucose and total N.

Biochemical Work.

The application of chemical methods by trained chemists to the problems of disease may be called a recent event, since it took place,

apart from isolated pioneer efforts, well after the student days of the older members of the profession. As regards the psychoses, this application may be called a thing of yesterday. I may be doing the German and Italian psychiatric clinics an injustice, but I cannot recall any outstanding communication on the subject in question prior to 1904. I mention that date, as it was then that Otto Folin, whose contributions to bio-chemical work have been so numerous and weighty, published, with Shaffer, the metabolism studies (already referred to) which were carried out in the chemical laboratory (established in 1900) of the McLean Hospital for the Insane, Waverley, Mass. In 1901 a chemist was appointed to the London County Council's Asylums Service, in the person of S. A. Mann. Reference should be made to the work of Koch and Mann, which was a chemical study of the brain in healthy and diseased conditions. with especial reference to dementia præcox (28), and that of Pighini, upon organic metabolism in dementia præcox, published in *The Archives of Neurology and Psychiatry* (edited by Mott) in 1909. In more recent times chemical investigation in cases of the psychoses, and probably of disease as a whole, has been in the domain of bio-chemistry. In 1910 Dr. R. V. Stanford was appointed Research Chemist at the Cardiff Mental Hospital. Only those who have been in touch with this branch of investigation can appreciate the amount of spade-work which has been necessary to obtain accurate methods before any research could be undertaken. Above all, one should mention the elaboration of accurate micro-quantitative methods, essential where small quantities of material have to be dealt with. It is not surprising that up to the present bio-chemistry has been concerned, as far as our branch of work goes, with comparatively elementary research. But, with the growth of knowledge in physical chemistry, still more difficult fields must be cultivated. " Interest in the study of physical chemistry and of colloidal chemistry is steadily on the increase amongst biologists and medical men." Thus wrote Michaelis in 1920, in the preface to the first edition of his *Praktikum der physikalischen Chemie*. It must be an interest based upon sufficient knowledge of the subject to suggest to the chemist lines of research, and to enable the physician intelligently to follow the research.

I confess (envisaging the developments of the future) that I am an advocate of dichotomy in the matter of the "bio-chemist." Co-operation between the chemist and the physiologist (should we not add the biologist?) in association with the clinician and pathologist—herein lies the symbiosis to be aimed at. To a large extent, says Handovsky in a recent number of the *Deutsche medizinische Wochenschrift*, vital reactions are conditioned by physico-chemical

forces. Recondite problems are suggested by this observation, calculated to nourish that spirit of humility which should possess each of us. We have learnt that metamorphosis (fundamentally a matter of cell-growth) in the tadpole is profoundly influenced by hormones added to their fluid environment (*e.g.*, thyroxin), the action of which, again, is conditioned by the addition of electrolytes (*i.e.*, calcium, potassium—Zondek), which appear to play an important *rôle* at the cell-surface. Scholberg and I have found, from a large number of experiments upon rabbits, that the action of adrenalin, and of thyroxin + adrenalin, in increasing the output of reducing substances (amongst them glucose) in the blood is inhibited by calcium chloride. This, again, I would explain as the conditioning of hormonal action by the calcium-ion. Doubtless, other evidence could be cited in this connection. I am not aware that we know anything as to the relationship of the nervous system to these matters, but here are two physico-chemical problems to appeal to, or shall I say rather, to appal, the seeker after truth.

The following information has been obtained from work on biochemical lines. The statement of some that there is a hypoglycæmia before a fit has failed of verification in our laboratory. When a series of epileptics received a large dose of glucose daily in addition to their ordinary diet, the incidence of fits was not affected. Epileptic fits are not brought on by hypoglycæmia, and in this respect differ from the convulsions which may follow insulin treatment. Neither is there, in my belief, satisfactory evidence of alkalosis in the pre-paroxysmal state, as has been asserted. On the contrary, Claude and others (29) have established that when alkalosis is produced (pH 7·50, or slightly over) by injecting into the blood-stream carbonate of soda in dogs, the bearers of epileptogenic lesions of the Rolandic area, epileptic seizures do not result. Perhaps a toxin is required in addition.

These results are inconsistent with the statement (30) that epileptic attacks, said to be brought about by forced respiration in epileptics, are due to an alkalosis, produced by elimination of CO_2 in excess.

Drury and Farren-Ridge, and Holmström (cited by Mann (31)), found normal carbohydrate tolerance in epilepsy. In the course of a systematic investigation into the question of sugar-content of the blood and cerebro-spinal fluid in epilepsy, which formed part of research-work carried on with the aid of a grant from the Medical Research Council, we found that there was no consistent difference in the amount of blood-sugar before or after a fit, whether of the major or minor variety, or during the fit. In the cerebro-spinal fluid of the epileptic we found a higher sugar-content than the

normal average in the majority of instances; and this irrespective of the incidence of a fit, though a slightly higher reading was found during the fit. Glucose tolerance tests in epilepsy showed a normal reaction to an oral loading test in 10 out of 16 cases. The abnormal reactions showed delay in return to normal, or variations in concentration before such return. In the cerebro-spinal fluid there was, on the whole, a steady rise, so that when the consecutive blood-sugar hypoglycæmia is present, the cerebro-spinal fluid is richer in sugar than the blood. This bears out the observation of Halliday(32) that the cerebro-spinal fluid sugar curve, after glucose orally, rises more slowly than the blood-curve in normal persons and in encephalitics. This is an interesting contrast with what is noted in dementia paralytica. Taking the dextrose concentration-factor of the cerebro-spinal fluid as 0·6 for the normal average, epileptics on the whole were above this, while general paralytics were usually below. This may be due to defective functional capacity of the choroid plexus (? gland) in the latter.

As we know, a good deal of work has been done, and still more theorizing taken place, on the subject of the cerebro-spinal fluid—its origin, functions and disposal (there is still no complete knowledge of these matters), and on the function of the choroid plexus, with its cellular lining. The plexus-cells would appear, as far as we know at present, merely a part of the " barrier " or " screen " between blood-stream and nervous system, there falling to be considered in this structure the glia, the cerebro-meningeal capillaries (possibly their endothelium principally), the ventricular ependyma, the pia. This " barrier " is believed in health to hinder the penetration of toxic substances into the brain-substance. The subject is well dealt with by Büchler (33), of the Neuro-Psychiatric Clinic in Budapest. Up to the end of 1924 there was no satisfactory method of testing the degree of permeability of the " barrier," but the bromide-method of Walter (34), of the Neuro-Psychiatric Clinic in Rostock-Gelsheim, as modified by Hauptmann (35), has been favourably reported on by various workers, including Büchler. This consists in giving ·01 grm. sodium bromide per lb. of body-weight three times a day for 5 days, and then withdrawing blood and cerebro-spinal fluids. The serum is allowed to separate, 4 c.c. of it being required, to which is added aq. dest. 8 c.c. Of the cerebro-spinal fluid, 8 c.c. are taken. The protein is precipitated by trichloracetic acid. To 5 c.c. of the perfectly clear filtrate in each case 1 c.c. of ½% of gold chloride solution is added. According to the amount of gold bromide formed, a yellow or brown colour results. This is compared with standard solutions of 1 : 6000 to 1 : 1000 in a colorimeter. A permeability-quotient (P.Q.) is

obtained by dividing the serum-bromide by that in the cerebro-spinal fluid. In healthy persons this quotient is very constant, and is taken as 2·90 to 3·30 by both Walter and Hauptmann.

The principal interest of this work seemed to be in the suggestion of Walter and Hauptmann that a difference in permeability of the "barrier" appeared to exist as between patients in the so-called schizophrenic group and those suffering from functional or symptomatic psychoses, the former manifesting a diminished permeability (therefore a higher quotient), the latter an increased permeability (therefore a lower quotient). It was clear to these authors that more work required to be done before this difference could be confirmed. Hauptmann and Walter, later also Büchler, found often (the first-named in 78%) a diminished permeability of the "barrier" in schizophrenia. No parallelism has been found between the clinical picture and the P.Q. The diminished permeability of the "screen" in this group is shown by Büchler to be more marked in the younger years.

I have examined 25 cases of schizophrenia and 28 cases of "functional" mental disorder. Of the former, 20 were done twice. The average quotient of the first time (25 cases), 3·35; ditto, second time (20 cases), 3·18; final average, 3·26.

None of these cases was recent in admission or origin except 4. All were in good health except 4. Eighteen were under 30 years of age; of the remainder, all were 36 or under.

Of the "functional" cases, the average quotient the first time (28 cases) was 2·9; ditto, second time (20 cases), 2·9; final average, 2·9. The great majority were recent admissions, and the disorder was of recent origin. Fifteen were cases of mania or melancholia; the rest, confusional disorder, hallucinatory, delusional or obsessional states, and 2 were found not insane.

Fifteen were under 35 years of age; 6 from 35–40; 7 from 40–58; all were in good health, excepting 4; several of those examined a second time were improved mentally; but the quotient obtained had no bearing upon the altered state.

From the work of Büchler, and also of Jacobi and Kolle (36), it may be concluded that, although in a large proportion of cases the P.Q. is increased in schizophrenia—and in a larger proportion than in functional symptomatic psychoses—the permeability-test will not serve as a means of diagnosis between these conditions. My results are in agreement with this.

The question of the permeability of the blood-liquor screen has to be considered in conjunction with that of plasma colloidal content. Kant (37) refers to the relationship between increased permeability of the screen and lability of plasma on the one hand,

and a diminished permeability of the screen and stability of plasma on the other.

The bromide-method shows well the increased permeability of the " screen " (meninges, vessel-wall, etc.) in dementia paralytica, these cases showing a diminished quotient.

A valuable contribution on " Blood-Sugar Studies in Mental Disorder "—based upon 152 cases—has been made by S. A. Mann (38). In common with all investigators who have studied this subject, he finds that in a large proportion of early and chronic mental cases there is a disordered carbohydrate metabolism, as shown by a sustained hyperglycæmia following glucose ingestion. This abnormality is not associated with any particular mental condition, but is more frequent in states of melancholia, and especially stupor. Even when blood-sugar levels in mental disorders approximate to the original fasting value about 2 hours after glucose ingestion, the curves are not, in general, similar to normal curves. The fasting level does not show any marked variation from the normal. Lorenz (39) also finds the fasting level normal in mental disease in general, but excepts dementia præcox. He, too, describes a hyperglycæmia in response to a glucose tolerance test in the depressed phase of manic-depressive insanity, and in active cases of catatonic dementia. Otherwise, the response is generally within normal range. Kasanin (40) remarks that the findings of various authors are not consistent. His paper deals with the special case of schizophrenia, and in regard to this his conclusion, based upon his series of 33 cases, and on 154 cases from the literature, is that the average glucose-curve in the blood falls well within the normal limits, although the percentage of abnormal curves is much higher than in healthy subjects.

Our contribution to this matter at Cardiff may be summarized thus: Cases of schizophrenia, 25, all chronic and in good health; 23 of them between 19 and 34 years of age; 2 aged respectively 39 and 40. The fasting blood-sugar was normal, except in 6. Response to a tolerance test (50 grm. of glucose by mouth) was only normal in 6 out of the 25, abnormal in 19. The abnormalities consisted in diminished or increased tolerance, or very poor reactions. Cases other than schizophrenia, of a functional, recoverable type: 25, all recent admissions, and disease of recent origin, excepting 5; in good health, 11; reduced, 14; 12 of the 25 were aged from 19–33 years, the remainder (excepting 4) were under 45. In these, again, the fasting blood-sugar was normal, except in 5. Response to the glucose tolerance test was abnormal in 20. The abnormalities consisted in very poor reactions or diminished tolerance. Our results in regard to the fasting blood-sugar agree with those of

other writers; it was found to be in general normal in amount. We found the response to the glucose tolerance test normal only in the minority of cases, whether of schizophrenia or of the functional psychoses.

The urine-sugar examined at the same time as the fasting blood-sugar by the Benedict test (as modified by Millard Smith), as well as colorimetrically, was found higher than normal in 21 out of 29 cases. The urine was examined also at the end (three hours) of the tolerance test, but the results are at present difficult to interpret.

In the above examinations the Folin-Wu method of estimation was employed.

The very poor reactions (low curves) which we obtained in a number of cases are puzzling.

The following considerations, cited from an article by Myer (to which for details I would refer you) in the *Klin. Wochenschr.* of December 17, 1926, are of interest in this connection. 10 grm. of levulose by mouth produce hyperglycæmia in normal persons. This begins to be noted at a time when absorption from the gastro-intestinal tract cannot have occurred. Therefore the rise in blood-sugar is not due to the sugar ingested, but rather to a glycogenolysis produced by stimulation of the gastric mucosa. This stimulus works by way of the vegetative nervous system. There is a group of patients, free from liver disorders, which reacts to the levulose by a hypoglycæmia. These patients show lability of the vegetative nervous system, as evidenced by such signs as the following: Vagotonic type of adrenalin pressure-curve, positive oculo-cardiac reflex, respiratory arrythmia, dermographism, cold and damp hands and feet, spastic conditions of the bowel, with constipation, gastric hyperacidity, attacks of diarrhœa after psychical excitement, vaso-motor excitability, bronchial asthma. Some of these are improved by atropin. These are so-called vagotonic indications. The hypoglycæmic curve in these cases can be altered to a normal one by subcutaneous injection of 1 mgrm. atropin when the levulose is given, atropin alone not affecting the curve. This action of an anti-vagotonic drug appears to point to an important *rôle* of the vagus in blood-sugar regulation in these cases—an indication which is confirmed experimentally, electrical stimulation of the vagus producing a considerable increase of glycogen in the liver. This electrical stimulus is represented in the human experiment by the levulose. In the "vagotonic" type of patient, the stimulus, as in the experimental animal, is judged to lead to a storage of liver-glycogen, and, consequently, to fall in the blood-sugar.

A sharp distinction between "vagotonic" and "sympathicotonic" is, it is recognized, indefensible, but it is certain that many of our patients present stigmata referable to the vegetative nervous system, like those above mentioned. The conditions of the sugar test are, of course, not identical in these experiments with those of the usual clinical method; but the considerations adduced justify the reflection that the anomalous results in a sugar tolerance test in many psychotic cases may be referable to the influence of the vegetative nervous system. The statement of Myer *re* levulose is at the present time being tested in our laboratory at Cardiff.

As is known—and the subject is dealt with by Van Slyke and his associates (41)—there appears to be, in their words, "a definitely determinable, though small, amount of reducing substances in the blood which cannot be attributed to glucose. The exact nature of these substances is not definitely known . . ." After treatment of the blood under conditions that lead to complete destruction of glucose, these workers found in normal blood a residue of reducing substance, other than glucose, which showed a reducing power for copper equivalent to 0·01–0·03 (*i.e.*, 10–30%) of the glucose.

More recent methods than that of Folin and Wu for estimation of the sugar-content of blood give lower results by 17–25%, which are claimed to be more accurate, since these methods eliminate to a greater extent the interfering, non-glucose compounds (42).

According to Hector (43), in cases of severe diphtheria the concentration of the fasting blood-sugar is abnormally low "during the stage of toxæmia and acidosis." But in the psychoses, according to the evidence adduced above, it is usually normal; and all the evidence, as has already been intimated, points to a mild toxæmia, merely, in these states. This point is of interest.

In cases upon which functional tests are suitable, the state of the blood-sugar curve at periods during the course of the case should be ascertained, in order to learn what correlations, if any, obtain between the curve and the clinical condition.

The phosphorus- and calcium-content of the blood-plasma and cerebro-spinal fluid in the psychoses was investigated at our laboratory in Cardiff in 1925. Up to that time little or no information was available in regard to phosphorus in these states and a few references only existed in respect of calcium. It was necessary for our research chemists (Dr. Stanford and Mr. Wheatley) to devise accurate methods—after practical examination of existing ones—before this work could proceed. From an analysis of five preliminary cases they found (44) that the relative quantities of

inorganic, lipin and unknown P. are fairly constant in the blood. Of the total P., 85% is in the corpuscles. It is also interesting that the unknown P. is almost, if not entirely, confined to the corpuscles. It was established that, as regards the cerebro-spinal fluid, inorganic phosphorus is practically identical with total phosphorus, so that, whilst inorganic phosphorus was estimated in both fluids, total phosphorus required to be estimated in the plasma alone, calcium in both fluids. No reliable normal figures for phosphorus were available in respect of either fluid at that time. Knowledge as to calcium in serum in normal persons has some basis, and to this we were able to add information from six controls, plasma being investigated. For calcium in normal cerebro-spinal fluid there is even less information ; to this we added results from our six controls. With these reliable controls in both fluids we may compare the calcium figures given by Weston and Howard (45) in the two phases of manic-depressive insanity in serum and cerebro-spinal fluid. The average amount of calcium was practically the same in each phase, and there was no variation from the normal. Their figures closely resemble those of our controls. Our investigation embraced 31 cases of various kinds of insanity, and shows that neither in respect of phosphorus nor calcium is there any significant deviation from the normal in blood-plasma and cerebro-spinal fluid. In many of our cases repeated examinations were made. If this work is extended, endeavour should be made to obtain a sufficiency of control cases and as many instances of the acute and recent psychoses as feasible, and to repeat examinations.

Since the above investigation, the calcium and phosphorus content of the blood have been investigated in cases of mental disorder by Henry and Ebeling (46), who also find them within normal limits, with a relative increase in manic, a relative decrease in depressed and agitated states. Armstrong and Hood (47) reach the same conclusion in respect of calcium in serum (*i.e.*, that it is within normal limits).

In 17 cases of epilepsy normal concentrations of chloride, bicarbonate, inorganic phosphorus, total fixed base and calcium were found in serum and cerebro-spinal fluid by Hamilton (48).

The following experiment was made: Six patients were placed on the average institution (that is to say, a sufficient) diet, and the total and inorganic phosphorus in the blood-plasma, the inorganic phosphorus in the cerebro-spinal fluid and the calcium in the plasma and cerebro-spinal fluid were estimated. The same diet was continued for a period of eight days, and at the same time parathyroid extract was administered intra-muscularly as follows:

1st	day	. .	$\frac{1}{10}$ gr.
2nd	,,	. .	,,
3rd	,,	. .	,,
4th	,,	. .	,,
5th	,,	. .	,, a.m.
,,	,,	. .	,, p.m.
6th	,,	. .	,, a.m.
,,	,,	. .	,, p.m.
7th	,,	. .	,, a.m.
,,	,,	. .	,, p.m.
8th	,,	. .	$\frac{1}{6}$ gr. p.m.

$\frac{12}{10}$ gr. total in each patient.

The blood-plasma and cerebro-spinal fluid were again examined for the above constituents, on the morning of the 9th day, with the following results:

Effect of Parathyroid Extract on Phosphorus and Calcium in Plasma and Cerebro-spinal Fluid.

Case.	Mgrm. %.									
	Plasma, total.	% change.	Plasma, inorganic.	% change.	Cerebro-spinal fluid, inorganic.	% change.	Plasma calcium.	% change.	Cerebro-spinal fluid calcium.	% change.
A. (before) . .	10·5		3·4		1·3		11·1		3·8	
(after) . .	10·0		4·0		1·2		10·8		4·7	
		−5		+18		−8		−3		+24
B. (before) . .	12·4		3·9		1·3		9·1		4·1	
(after) . .	10·5		3·5		1·3		9·3		5·0	
		−15		−10		0		+2		+22
C. (before) . .	11·0		4·2		1·5		10·3		4·6	
(after) . .	10·5		3·5		1·5		10·0		4·8	
		−5		−17		0		−3		+4
D. (before) . .	10·4		3·6		1·3		9·7		5·0	
(after) . .	11·6		3·8		1·2		9·5		4·8	
		+12		+6		−8		−2		−4
E. (before) . .	13·5		4·6		1·4		10·2		4·6	
(after) . .	11·5		3·5		1·3		9·0		4·6	
		−15		−24		−7		−12		0
F. (before) . .	8·3		3·0		1·5		9·3		4·9	
(after) . .	7·1		3·0		1·5		8·2		5·1	
		−14		0		0		−12		+4

The parathyroid did not, therefore, have any characteristic action, and more especially it did not produce any increase (unless a fugitive one, not present when the fluids were withdrawn) in the

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calcium content of the plasma or cerebro-spinal fluid, except in the latter in two instances.

The extract used was supplied by a well-known firm, and was made by Collip's method.

The phosphorus and calcium were estimated by methods described by Dr. R. V. Stanford in *The Biochemical Journal*, vol. xix, No. 4, 1925. (See also the *Journal of Mental Science*, January, 1926, Scholberg and Goodall.)

Another line of chemical investigation—still in progress, with the financial aid of the Medical Research Council—at our laboratory at Cardiff has for its object the determination of the proportion of the various nitrogenous constituents of the plasma and cerebro-spinal fluid in cases of mental disorder. Up to the present 38 cases have been dealt with (plasma), and 40–44 cases for different constituents of the cerebro-spinal fluid. The following were investigated in the cerebro-spinal fluid: Total N, non-protein N, urea N, creatine N, so-called "creatinine" N, amino-acid N, and uric acid N. From these the protein N and the unknown N were calculated by difference. Simultaneously the same constituents, with the exception of total N, were estimated in the plasma. And total N, urea N and ammonia N in the urine (24-hours' specimen), these being the chief forms in which N is present in urine. It will be seen that we dealt with the chief forms in which non-protein N is present in the plasma and cerebro-spinal fluid. Our patients were in bed for three nights and two days on a standard diet, calculated to yield 15 calories per lb. of body-weight. The fluids were withdrawn in the fasting state before breakfast. Kidney-function tests (urea-concentration and Mosenthal) were done in all cases, in addition to ordinary clinical urinary tests, to establish that any excess in nitrogen found in the plasma and cerebro-spinal fluid was not ascribable to damaged renal function. The ages of our cases ranged from 21 to 52 years, 10 being 35 and under; 13 were over 45. All were males except 8. As far as normal figures are available from Folin's *Laboratory Manual* (3rd edition, 1922), we have used these for comparison in respect of the plasma. These figures were obtained from 12 young men after a night's fast. The diet is not stated. To the best of our belief, no normal figures for the constituents estimated are available as regards the cerebro-spinal fluid, and probably the work now recorded is the first reliable detailed work on this fluid. Levinson's figures in his 1923 work on the cerebro-spinal fluid we do not find helpful. Therefore, as controls in this case we used average figures from five healthy quiet patients employed on the land, and one healthy patient, also so working, and who had

recovered some time since from an attack, probably alcoholic in origin. Our cases may be placed in three clinical groups: Dementia paralytica (9 cases), chronic mental disorders, but with definite mental disturbance (13 cases), acute and recent ones (20). I shall do no more than summarize our main results, thus:

Cerebro-spinal fluid.—The great majority of cases show abnormal figures of total N. The figures for dementia paralytica are high; other figures vary, but are mostly low. Protein N is high in dementia paralytica. Total non-protein N is low in this; not abnormal in other disorders. The well-proved increase of protein N in dementia paralytica is not, therefore, accompanied by an increase in the other nitrogenous constituents, taken as a whole or individually. Urea N: High and low figures occur, but the majority are normal. Amino N is not abnormal. The figures do not distinguish recent from chronic cases.

Plasma.—Non-protein N figures are high. Urea N figures tend to be high. Amino-N figures are low. The figures are irrespective of the type of case. In 14 cases the unknown N is high in the plasma, the non-protein N being also high, and the urea N high or normal in these cases. These cases are both recent and chronic. Unknown N forms 20–40% of the total non-protein N (a high proportion). The percentage tends to be higher in dementia paralytica. As to what the unknown N—which is got by subtracting the sum of the various non-protein N constituents estimated from the total non-protein N—is, remains for investigation. In our later cases, suitable methods having been elaborated, uric acid has been removed from the unknown N and separately estimated. The amino-acid N forms 9–22% of the total non-protein N of the plasma, the average value being 13·5, which compares with an average of 21 calculated from Folin's figures for normal persons. This is in keeping with the low absolute value of this constituent. Of the total non-protein N of the cerebro-spinal fluid, the amino-acid formed 3·5–6% (except in 2 cases). The amino N figures in plasma for our cases of the psychoses in various forms lie between 3·0 –5·0, with an average of 4·0; 0·7 and 1·3, with an average of ·95 for the cerebro-spinal fluid (all figures indicate mgrm. %).

Folin's normal figures for amino N in plasma are 4·4–6·2, average 5·4. Wiechmann's (49) figures, 4–6·1. Our psychotic cases (as just stated), 3·0–5·0, average 4·0. The psychotic cases, therefore, have a rather lower average. In the cerebro-spinal fluid the control and psychotic figures are practically the same.

Greene, Sandiford, and Ross (50) examined the amino N in the *whole blood* in 20 normal persons, and found the average to be

6·37 mg. % (4·8–7·8 mg.%). Blood samples were taken before breakfast. The authors state that according to Hammett, practically the same amino N content is found in blood samples taken from three to four hours after a meal as in fasting samples. In our cases (the patients having been, as previously stated, on a fixed diet) the blood was removed before breakfast, the patient having had nothing to eat since tea the night before. The authors just cited did not find any deviation from amounts found in the normal blood in a series of observations covering 20 various pathological states.

In general it appears that the quantity of amino N in the blood is maintained within normal limits with remarkable constancy.

We considered it was more logical to examine plasma than blood for this substance, since we were concerned with the circumambient fluid, and not with the internal processes of any living cell, mobile or fixed.

It is concluded from the above that there is no noteworthy deviation from the normal in the amino N figures of the plasma and cerebro-spinal fluid in our psychotic cases.

The low (absolute) figures in which the amino N is present in the cerebro-spinal fluid in normal and psychotic cases might be adduced as an argument against the view that this fluid has nutrient properties. Although variations occur in the chief N constituents, the amino N figures are pretty constant in both fluids in all classes of psychotic cases dealt with, including a special case (about to be referred to) with evidence of arterial disease, in which the chief N figures in both fluids are greatly in excess.

The high protein content of the cerebro-spinal fluid in cases of organic brain disease or lesion would indicate that this fluid is a vehicle for removal of breakdown products.

The examination of the N partition in these cases brings out that when protein is increased in the cerebro-spinal fluid, the case is invariably one of gross organic lesion of the brain-substance (*e.g.*, dementia paralytica, localized cerebral hæmorrhage). Certain cases which failed to pass renal function tests, and, therefore, were excluded from our series, although they showed excess of non-protein nitrogen in plasma or plasma and cerebro-spinal fluid, showed no excess of protein in the cerebro-spinal fluid.

The special case alluded to above was that of a male, æt. 52, with arterial disease; there had been two strokes, recovered from, and probably chronic renal changes. He exhibited mental hebetude, with faulty personal habits, and a physical condition suggestive of bulbar paralysis. It will be seen from the table hereunder that the chief N figures in both fluids are greatly in excess compared

with the controls. Yet the amino-acid figures in plasma and cerebro-spinal fluid remain normal.

Plasma.	Non-protein N.	Urea N.	Creatine N.	"Creatinine" N.	Uric acid N.	Amino-acid N.	"Unknown" N.
Special case:							
February 25, 1926 .	50·2	21·6	0·80	0·60	..	3·4	23·8
May 3, 1926 . . .	78·4	44·2	0·27	0·66	..	4·0	29·3
Average of 4 chronic, healthy, working adults . . .	28·1	14·2	0·35	0·38	..	4·1	8 9
One sane, healthy, working adult	28·0	16·0	0·14	0·29	1·5	2·9	7·5
Folin	24·7	12·4	..	..	..	5·3	..

Cerebro-spinal fluid (clear and colourless).	Total N.	Non-protein N.	Urea N.	Creatine N.	"Creatinine" N.	Uric acid N.	Amino-acid N.	Protein N.	"Unknown" N.
Special case:									
February 25, 1926 .	44·7	31·8	21·4	0·16	0·42	..	0·8	12·9	9·0
May 3, 1926 . .	69·4	48·7	40·3	0·04	0·41	..	0·9	20·7	7·1
Average of 5 chronic, healthy, working adults	26·0	17·7	12·9	0·8	0·35	..	1·1	8·3	3·3
One sane, healthy adult .	26·8	24·0	16·0	0·1	0·3	0·2	0·8	2·8	6·0

This man's fluids were examined twice, it will be noted—on the first occasion, seventeen days after admission, and while still very ill mentally and physically; on the second, twelve days before he was discharged, being quite well in mind, and physically much improved. If the mental symptoms present when the fluids were first examined had been in any way due to the N-retention they should have been present at the second examination, when, as the table shows, the evidence of retention of the more important constituents was more marked.

This case seems of special interest, in that it can be but seldom that a clinical condition of the kind described has been investigated in respect of N-partition in cerebro-spinal fluid, blood and urine so fully, and, in the second place, it points to the need of caution in correlating chemical conditions with psychical manifestations. If a fall in the N figures had accompanied the clinical improvement, the chemist would, perhaps, have been in a position to supply a plausible explanation.

Lastly, as regards the urine in the mental cases examined (31 cases), control figures—minimum, maximum and average—are available from Folin's "Analysis of 30 'normal' Urines" (51). With very few exceptions the total N and urea N are low in all our cases; our resting calorie diet was lower in protein-value than the liberal protein diet of Folin. But the total N and urea N are as low in many of his cases as in ours. With these low urine figures go the figures for non-protein N and urea N in the plasma, which are high compared with Folin's normal figures before mentioned. And these results were obtained in patients whose kidneys were acting adequately according to kidney function tests.

These apparent anomalies of protein-metabolism, shown by this study of blood-plasma, cerebro-spinal fluid and urine, can at present merely be recorded. Folin, it will be remembered, found abnormalities of metabolism from his classical study of the urine of the insane.

With the progress of scientific medicine, especially aided by the contributions of bio-chemistry, it is to be expected that an ever-increasing demand will be made upon us in the matter of examination of recent cases of disease. Already, if we are to do what is right by cases of so-called mental disease, the number of medical and research workers on the strength at our mental hospitals is pitifully inadequate. When one is asked the time-worn question, "How many patients should there be to one medical officer at a mental hospital?" (I speak now of the public institutions), one replies, "Ask, rather, how many workers, and what sort of workers, should there be to concentrate on each newly-received case judged to be recoverable." My view is that the time is already upon us when it is for practical purposes very difficult for any public mental hospital to collect, maintain and retain the team of workers which thorough physical investigation of a case of disease demands. Very rare exceptions may be allowed, as where the mental hospital is very near a University centre, with medical school and general hospital available, and a degree of collaboration has been established. It is obvious that the necessary combination of workers will more easily be found in future psychiatric clinics—an integral portion of the general hospital.

In addition to a case-taking scheme which, as at many mental hospitals now, is comprehensive, functional tests are required, and special examinations, thus, to mention some: Blood-urea and urine-urea, quantitatively; fasting blood-sugar, glucose-tolerance test, quantitatively, contemporaneously with urine-sugar; CO_2-combining power of plasma, with contemporaneous urine for "acetone" bodies; kidney-function tests; fractional gastric test-meals; set

of radiograms showing progress of a barium meal and position of digestive tract; rhinological and gynæcological examinations; dental ditto; basal metabolism; total blood-corpuscle counts, and differential white-cell ditto, hæmoglobin percentage, colour index; reactions to adrenalin and pilocarpine. At Cardiff our chemical laboratory is but little involved in the above routine, and will come more on the strength as more recondite work—thus, the hydrogen-ion content of body-fluids—is taken up.

Do the cases brought to a neuro-psychiatric out-patient clinic require examination on the above lines? In my experience the majority do. Of what use, then, is such a department in the absence of beds? Of some use in, say, 30% of cases.

In conclusion, the following results of the examination of the CO_2 combining power (van Slyke and Cullen) in a series of freshly-admitted psychotic cases are cited:

These cases (40) come under the following clinical designations; melancholia, 9; mania (Graves's), 1; dementia præcox, 5; confusional state, 8; mania, 3; emotional state, 2; stupor, 1; delusional state, 7; simple-minded (? post-encephalitic), 1; G.P.I. mania (florid), 2; stupor-melancholia, 1. Their physical condition was reduced, in the usual way that it is reduced in patients admitted into these institutions. They had no other specific disease. Of these patients 33 out of 40 had CO_2-combining power of 53 to 42, indicating a mild acidosis. Acetone bodies in the urine in only 4. In only 4 cases was the combining power above 53; 2 were respectively 37 and 41. One showed a figure of 29, which indicates severe acidosis, and in her urine acetone bodies were well marked.

I desire to express my thanks to my colleagues at the Cardiff City Mental Hospital, and especially to Dr. Scholberg, Consulting Pathologist, and Dr. R. V. Stanford, Research Chemist, and his assistant, Mr. Wheatley (who were responsible for the chemical work), for their valuable collaboration.

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*The Induction of Abortion in the Treatment and Prophylaxis of Mental Disorder.**

By Lt.-Col. J. R. Lord, *C.B.E.*, M.D., F.R.C.P.E., President of the Royal Medico-Psychological Association (1926–27).

My attention was sharply drawn to this subject by the submission to me recently of a case for decision as to whether abortion should or should not be induced as a prophylactic measure in regard to the possible recurrence of mental disorder.

I will first give you some details of this case, how it came to be brought to my notice, and the action I took regarding it.

She was admitted to a mental hospital late in 1923, single, aged 21. Her weight was 7 st. 6½ lb., and height 5 ft. Menstruation had been delayed until the age of 19, and had been slight and very irregular, and had occurred only occasionally with 4 to 6 months' intervals. Secondary sexual characteristics were scarcely at all present.

She passed the fourth standard at 14 years of age, being very slow to learn. School reports stated that she was backward in her studies, and with difficulty learned to read and write, and was dull and lazy. There was obviously a degree of congenital feeble-mindedness.

Her history for the past eleven years or so presented a train of schizoid symptoms, and ultimately her conduct became so outrageous that she could no longer be kept at home. For three months she had had horrible crawling sensations in her head, causing phases of acute confusion.

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* Being the opening speech of the discussion on this subject held at a meeting of the South-Eastern Division, Stone, Dartford, on April 14, 1927.