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The Significance of Acidosis in Certain Nervous Disorders.(1)

By B. H. SHAW, M.D., Medical Superintendent, County Mental Hospital, Stafford.

THE clinical evidence of acidosis is the detection of acetone bodies in the urine. Acetone is formed from diacetic acid by the splitting off of carbonic acid, the origin of diacetic acid being in part from fats and in part from proteins. Oxybutyric acid is also formed from diacetic acid by reduction, consequently the presence of acetone bodies in the urine always means that acidosis is taking place. A delicate test is that known as Rothera's, which is quite simple, and will detect acetone in minute dilution:

To about a gramme of ammonium sulphate in a test-tube add a few cubic centimetres of urine, a couple of drops of a freshly prepared solution of sodium nitroprusside, and a cubic centimetre of strong ammonia. A purple colour develops. Nitro-prusside can also be used to detect diacetic acid.

Synchronously with the production of acidosis there is a retarded oxidation as the sodium carbonate of the plasma, which normally carries off the CO_2, tends to be neutralised, and as a result tissue-cells, for their own protection, set free autolytic enzymes of various kinds, which attack the proteins and lipins of the cell itself in order to liberate ammonia, with the object of neutralising the cellular acidity; imbibition of water by the cell-wall now occurs, and the slowing down of all cellular activities; fatigue consequently comes on much sooner with reduced alkalinity.

Acidosis is by no means infrequently met with. The already published literature on the subject gives the following states in which it occurs:

(1) Read at the Staffordshire Branch meeting of the British Medical Association, February 26th, 1920.

Diabetes mellitus, fevers, nephritis, phosphorus poisoning, fasting, grave anæmias, deranged digestion, auto-intoxication, chloroform and ether anæsthesia, and what is known as biliousness.

I frequently meet it in my practice and many fresh admissions are found to suffer from it. It is especially frequent in acute delirium, melancholia, confusional and stuporose states, and epilepsy. It may indeed very possibly be an important ætiological factor in the production of epileptic states, for reasons to be referred to later. The following notes are taken from two recent deaths, resulting from extreme acidosis:

(1) E. J—, a mischievous, weak-minded boy of impulsive tendencies, æt. 15, admitted in September, 1917. He was well nourished and took his food very well indeed. He had had no fits previously. During the night of December 30th, 1919, he had a severe typical epileptic fit, and lapsed into a condition of cerebral irritation with paresis of his legs and conjunctival injection. Specific gravity of urine 1024; no albumen or sugar, but strongly positive to acetone. He was put on alkaline treatment and improved, the acetonuria disappearing, and he continued to take his food well. On January 10th he again developed strong acetonuria, which did not yield to alkaline treatment, and he died at 9.40 a.m. on the 16th. *Post-mortem:* Intense minute injection of the pia arachnoid in a patchy fashion, especially marked over sulci and along veins, one large patch extending over the vertex of the left hemisphere; numerous punctæ cruentes on section of the cerebral tissue; strong acetone reaction in cerebro-spinal fluid and blood. Microscopical examination showed minute vascular engorgement, diffuse and central chromatolysis of the neurone body and degenerative changes in nuclei—in other words, primary degeneration of the nerve-cell. The suprarenal glands showed some congestion and fat deficiency; other organs apparently normal.

(2) J. H—, a well-developed man, æt. 49, admitted on February 4th in a state of acute confusion, had been ill for six weeks prior to admission. He was, on admission, in a state of restless, noisy excitement, continually wet and dirty, rendering it impossible to collect his urine for examination. He was put on milk and other extra diet, which he took satisfactorily. He was extremely feeble when admitted, became gradually weaker, and died at 2.30 a.m. on the 10th. *Post-mortem:* Cadaver in good condition, marked opacity and thickening of the pia arachnoid with much recent minute injection and patchy ecchymotic areas. Brain tissue showed numerous punctæ cruentes on section. Acetone reaction strongly marked in cerebro-spinal fluid, which was in excess, in pericardial fluid and in the blood. Microscopical examination showed engorgement of vessels with some minute extravasations, diffuse and central chromatolysis of cells, nuclear changes and absence of pigment. Suprarenal glands softened, scanty fat; liver somewhat fatty; other organs normal.

A certain amount of acetone and diacetic acid will be found in ordinary *post-mortem* decomposition, but nothing like the quantity present in the body-fluids in cases of death from acetonæmia. The examination, of course, must be done as soon after death as possible.

In the case of the boy J—, his first fit occurred at a very usual age for the onset of so-called idiopathic epilepsy, also there was in this case no question whatever that inanition had anything to do with the causation; the boy looked after himself very well indeed in that direction.

Dealing with the *post-mortem* appearances in both these cases, I may state that in *post-mortem* examinations on mental cases it is the exception to find a normal transparent pia arachnoid. Secondly,

in long-standing cases of epilepsy almost the only change met with may be a thickening and opacity or milkiness of the pia arachnoid; this thickening and opacity I regard now as most probably due to congestive attacks resulting from acid intoxication. These congested areas are most pronounced over the vertex, where the membrane is thickest and the underlying neurones mainly motor. Thirdly, after death in *status epilepticus* there is intense congestion of the membranes, and the cells show the profound structural changes of primary degeneration—structural changes which I have shown to be also present in the cases mentioned. It is of interest to note here that the meningeal appearances in these cases are very similar to many I have seen in the Balkans as a result of malignant malaria, and in which the symptoms indicated intense toxæmia, no doubt due to deficient oxidation as a result of the destruction of vast numbers of erythrocytes, and also to the hæmoglobin and oxyhæmoglobin set free in the plasma behaving as weak acids. Addison, Lusk, and Graham consider that the rise in heat-production in severe anæmias is due to the pathological production of lactic acid from carbohydrates in consequence of an inadequate supply of oxygen to the cells. Recently I have had two cases of confusion following malignant malaria contracted at Salonica, one of whom had definite acidosis periodically while here.

I will now mention briefly some cases which came recently under my notice:

(1) J. P—, a young woman, æt. 22, single; case of acute delirium of three days' duration prior to admission; *cause*, mental shock; no insanity in family. Acetonuria on admission, sp. gr. 1030, no albumen or sugar present; under treatment practically recovered in three weeks.

(2) D. P—, woman, æt. 47; four previous attacks, first at age of twenty-three, simple melancholia with acute confusional periods, which synchronise with acetonuria; takes her food well, and in good condition. I may say that with her last acetonuric attack tubercle bacilli and slight albumen appeared also in the urine, neither of which can be found now. She responds very well to alkaline treatment.

(3) N. W—, woman, æt. 42; married; acute confusion, acetonuria on admission; *cause*, over-work and worry; history in this case of not taking her food prior to admission. Under treatment.

(4) V. H—, woman, æt. 36, married; melancholia with acute confusional attacks synchronising with acetonuria and responding well to alkaline treatment; always takes her food well; *cause*, worry and mental shock.

(5) E. S—, woman, æt. 48, single, no history; melancholia, acetonuria on admission; takes her food but otherwise very resistive.

(6) E. L. S—, man, æt. 29; stupor; admitted with acetonuria, very intense reaction; on alkaline treatment acidosis cleared up; mental condition not appreciably improved as yet. Possibly the injury to the neurone in this case precludes recovery.

(7) G. H—, æt. 30, military case; confusional mental condition associated with acetonuria, pulmonary tuberculosis also present; *cause* given as stress of campaign.

(8) W. R—, man, æt. 33; violent epileptic; acetonuria present with outbreaks of excitement; slight trace of sugar on one occasion; said to be a heavy drinker.

(9) S. K—, man, æt. 56; simple melancholia; a little while ago got a sudden attack of acute confusion and violence synchronising with strong acetonuria;

much improved under treatment; *cause* given as over-work; always takes his food satisfactorily.

(10) H. P—, boy, æt. 17; strong family history of insanity; father, two brothers and sister have been insane; on admission much acetone present in urine; in a state of acute excitement and quite incoherent; rapidly recovering under alkaline treatment.

(11) F. D—, male, æt. 20; case of masked epilepsy; acetonuria present during attacks.

(12) S. G—, æt. 28; epileptic, very violent, and impulsive; acetonuria during attacks.

In cases which recover it is noteworthy that the improvement synchronises with diminishing acidosis. These are only a few of many cases: For example, acetonuria has been present in ten out of the past twenty-five admissions here and the mental disorder in all ten was of the confusional type. With the exception of four of the above-mentioned cases who were recent admissions, fasting could be excluded as an ætiological factor.

I must now refer to the direct effect of acetone bodies and bile acids *in vitro* on red blood-corpuscles. If red corpuscles are washed and incubated at blood temperature with small dilutions of these substances they are soon hæmolysed; this simply means disintegration of the cells. Taking into account the other still more destructive ferments present in acidosis, it is obvious that these substances in the blood and body-fluids must have a most irritative and disastrous effect on tissue-cells. This is already evidenced by the degenerative cell changes noted in the *post-mortems* alluded to. If the acidosis is intense or continued for a length of time, or if the patient gets frequent recurrences, permanent damage to the neurones must ensue.

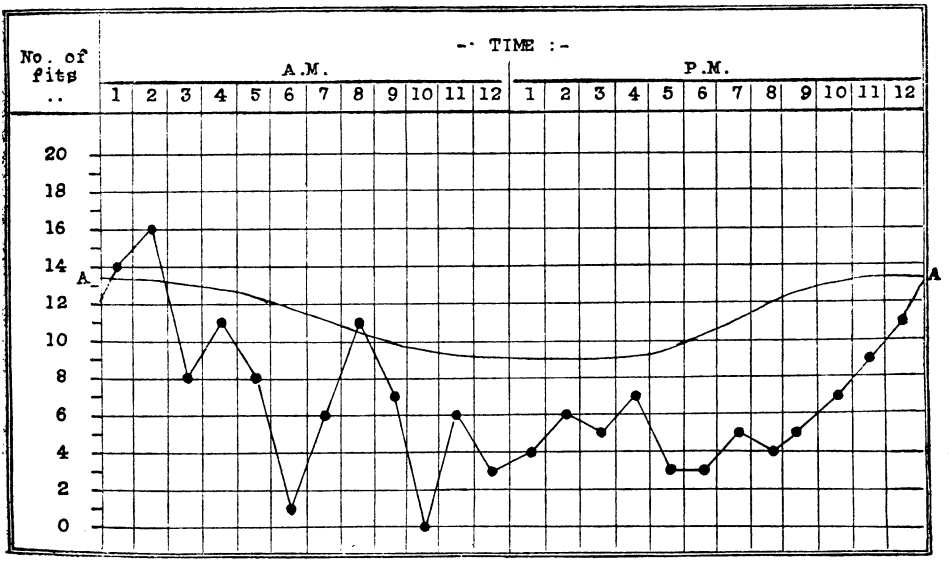
Now, as regards the varying nervous symptoms met with at different ages in acidosis, we have to consider the action of cholesterol, which is very soluble in acetone. The adult human brain contains an extraordinarily large amount of this substance—practically 2 *per cent.* of wet tissue—but in children there is relatively much less; thus, in a child of three months old there is only ·69 per cent. It can be shown *in vitro* that this substance has a protective function on erythrocytes with regard to the action of hæmolytic agents such as autolytic ferments and acids. It may therefore be assumed that its presence in the brain in such large amount indicates a similar protective action as regards the delicate neurone; any excess, therefore, of acids or autolytic enzymes in the blood of young persons might readily lead to different nervous symptoms and more serious neuronic irritation than would occur in later years, when more protection would be available for the neurone by the increased amount of cholesterol present. It must be added that the serum of infants is slightly less alkaline than that of adults, and that the carbon dioxide tension in the alveolar air of infants is lower, probably due to more active metabolism.

Referring to ferment action I have found that the diastatic content of urine is increased in acetonuria. Reducing the specific gravity in all cases to 1003, normal urine shows a diastatic reaction of 5 to 10 $\frac{38^\circ}{30}$, that is, when incubated at 38° for 30 minutes 1 c.c. of urine will convert 5 to 10 c.c. of 1 per mille starch solution into sugar. In acetonuria the diastatic content is somewhat higher, reaching at times as much as 25 or even 100 $\frac{38^\circ}{30}$. Again, it has been shown that pancreatic lipase, which is normally present in the blood, becomes hæmolytic if activated by fat; consequently the more fat there is in serum under certain conditions the greater would be the tendency towards cell irritation, such conditions being possibly cholesterol deficiency in the neurones or plasma or excess of circulating ferments. Here I would like to mention that the brain is the only organ in the body which contains no fat.

In reference to this I investigated sera from patients of different types of mental disorder as regards the effects on them of tryptic digestion. The sera were drawn at the same time of day in every case and primarily for syphilitic sera-diagnosis. The method I adopted was digestion of a definite amount of serum with extract of hog pancreas and bile for twenty-four hours at 37° C. and then neutralising with N/50 soda, using phenolphthalein as indicator. My results indicated that the serum in cases of chronic alcoholism, chronic melancholia and epilepsy showed a higher acid content as compared with others. I admit the difficulty of determining end-points accurately in such an investigation, but I took all possible care in the matter and only dealt with the sera by numbers. It is noteworthy that fits will occur in chronic alcoholism in a considerable number of cases. As further evidence of acidosis it may be mentioned that Haig and Krainsky independently determined that there was a marked fall in uric acid excretion prior to a fit, and Charon and Briche showed in 1897 that fits are most frequent during the night time, when the reaction of the blood tends towards acidity.

Reference to the time-incidence graph of fits occurring in this hospital during the past week will illustrate this. Again, it is well known that strongly nitrogenous diet increases the number of fits in epileptics; here again we have evidence of acidosis, for excessive proteid disintegration results in excessive acid production, the sulphur and phosphorus of the broken-down tissues being oxidised to form sulphuric and phosphoric acids, and these together with diacetic and oxybutyric acids neutralise much of the alkali of the blood, with resulting acidosis. This is equivalent to carbonic acid poisoning, and the sodium carbonate of the plasma which normally takes away the CO_2

from the tissues tends to be neutralised. It has been shown that carbon dioxide causes imbibition of water by the red corpuscles and an increase in their size, hence greater viscosity of the blood and a tendency to stasis in minute capillaries; it has also been shown that carbon dioxide protects these corpuscles and possibly therefore other tissue cells from the action of hæmolysins; it would thus seem possible that the presence of excess of carbon dioxide in the blood naturally resulting from the muscular spasm initiating an epileptic fit may have a certain protective action on the neurone—this is, however, by the way. Having in view the case of the boy E. J—, in which acidosis was



Time-incidence of 160 epileptic fits occurring during the past seven days. AA. Line indicative of reaction of blood. It normally tends towards acidosis during the late evening, and continues so through the night and early hours of the morning.

undoubtedly responsible for the fit, I have been for a little while back giving alkalies to a number of cases of epilepsy, and already I notice a decided reduction in the number of fits in certain cases. I also interdict salt. It must be remembered that the epileptics I am dealing with are very chronic cases in whom the neurones are educated up to the habit of taking fits on the smallest provocation. The best results are likely to be met with in early cases. It seems to me quite likely that a fit may be caused in early years by a serious attack of acidosis, which may soon pass away, but leave the cells in a certain state of irritation and liable to similar seizures with a succeeding lesser degree of acidosis; very slight stimuli may eventually bring a fit on, especially when a hereditary tendency exists. If this should be so it is of the

utmost importance to recognise the acidosis at once and deal with it before the habit is acquired.

Some six years ago I pointed out that in mental hospitals a high epileptic ratio is constantly associated with a high tuberculosis incidence and *vice versâ*; also that associated with a high ratio of epileptics in urban relatively to rural districts is a similarly high infantile and early childhood mortality from tuberculosis, convulsions and atrophy debility and marasmus, and in addition a correspondingly high proportion of occupied married women. In this connection I have to point out that acidosis favours microbic infection as one would expect: thus a large proportion of diabetics die of tuberculosis.

In 1889, von Mering and Minkowsky found that if the pancreas be completely extirpated, hyperglycæmia, glycosuria and acetonuria occurred, and a very interesting and significant fact was that in the animals experimented on vital resistance to infection was enormously reduced, so that it was extremely difficult to avoid infection in the operation or afterwards, and wounds healed slowly.

We may, therefore, take it for granted that acidosis predisposes to tuberculosis. A point worth noting in this connection is that excess of lecithin is present in the serum of tuberculous patients and also in those suffering from chronic insanity. Again, patients in asylums are very prone to microbic infection—witness what is known as asylum dysentery.

In 1898, Biedl showed that by throwing the thoracic duct out of circulation glycosuria resulted. Schaefer suggested that this was owing to the absence of a glycolytic ferment derived from the islets of the pancreas. I suggest, on the basis of amboceptor formation, that the ferment lacking would probably be derived from lymphocytes. Experimentally, Bullock determined that the amount of hæmolytic amboceptor varied directly as the number of mononuclear leucocytes. Now lymphocytosis is a feature of certain diseases, *e.g.*, tuberculosis, typhoid fever and malaria. It has also been shown by several observers to be present in epilepsy. In twenty-one cases of epilepsy—so far as I could judge uncomplicated by tuberculosis—I found a relative lymphocytosis present. This lymphocytosis I consider an evidence of increased ferment action. On this interpretation Biedl's diabetes would result from deficient ferment action owing to absence of lymphocytes; consequently hyperglycæmia will of necessity give rise to increased ferment action associated with reactive lymphocytosis.

In a leader in the *British Medical Journal* of February 14th last, reference is made to an article by Prof. Carmalt Jones, which appeared in *Brain* in 1917, in which he states that in considering a man's nervous system in neurasthenia the only physiological fact which struck him was the presence in the blood of an animal under the influence of fear of an

excess of sugar destined to supply the muscles with energy, and ascribed to increased secretion of adrenalin under the stimulation of the sympathetic; that the adrenals exercise some protective influence over cells so far as autolysis is concerned is shown by the fact that cobra toxin—which is a nervous toxin and hæmolytic to washed human erythrocytes, after being mixed with emulsion of adrenal cortex is rendered inert. It would appear, therefore, that the adrenals, as well as being concerned with sugar elaboration, have antidotal properties as regards autolytic agents; in sympathetic disturbances we may readily get this function in abeyance, and as a result serious interference with cell metabolism and consequent acidosis.

Blum observed in 1901, that subcutaneous or intravenous injections of adrenal extract in animals caused glycosuria. Herter and Wakeman also determined that quite small amounts of adrenalin applied to the pancreas provoked marked glycosuria. Carbohydrate metabolism is therefore apparently under the control of the sympathetic nervous system, as is also the protection of the cell from autolytic ferments. It may therefore be readily understood that disturbance of the sympathetic system may directly bring about a condition of acid intoxication. This may occur as follows:

Fright or anxiety produces hyperglycæmia; this is probably due to stimuli emanating from the brain, passing over the splanchnic nerves in part to the liver, inducing acetone formation and the splitting up of glycogen, and also to the suprarenals, causing a discharge of adrenalin. Constant action of this nature may lead to exhaustion of the adrenal tissue with resulting loss to the organism of the protection normally afforded against agents producing cell-autolysis. Further, adrenalin is *in vitro* readily precipitated by acetone, consequently the presence of acetone in the body-fluids directly inhibits the action of adrenalin.

Degenerative suprarenal changes are very constantly met with in *post-mortems* on the insane. In epilepsy Prior states that out of twenty suprarenal glands examined by him degenerative changes were present in fifteen; also, in addition to adrenalin being readily precipitated by acetone in solution, its normal destruction in the blood is inhibited by any tendency towards acidosis.

As regards a further possible source of acid production, I have been much struck by the frequent occurrence of pyorrhœa alveolaris in certain cases of mental depression and confusion, and have examined as regards sugar fermentation large numbers of streptococci from the roots of extracted teeth in such cases. All these organisms are strongly acid on litmus glucose, while negative on salicin, mannite, and lactose. This is certainly suggestive, and I am at present investigating the results of proper dental and vaccine treatment on such cases.

I wish now to refer briefly to some further experimental work.

Donath, Hahn, Massen, Pablow and Krainsky have found that a small quantity of blood taken from an epileptic who is suffering from a fit produced convulsions immediately when injected into a guinea-pig

or rabbit, but when drawn in the interval between the fits no effect resulted.

Hewlett states that the injection of epileptics' blood into animals is sometimes followed by severe hæmolysis.

Krainsky found carbamic acid present in the blood of epileptics in considerable amount.

As regards the toxic effects of human urine on animals different authorities arrive at various results, as is to be expected, taking into account the amount injected and its varying composition as regards time of excretion, etc. In large quantities normal human urine is toxic to animals. Bouchard demonstrated that the toxic dose corresponded to about 45 c.c. per kilogramme of the animal injected. I have found that urine from a case of acetonuria is strongly toxic when injected into rabbits. The following experiments will illustrate this and also throw light on the treatment.

I took two rabbits—both bucks from the same litter, and each weighing 3 lb. I injected intravenously into No. 1 2 c.c. of urine from a patient suffering from marked acetonuria, with the following result:

In a few minutes he became drowsy and lethargic, taking no notice of food, though previously feeding with avidity. Inco-ordination of hind legs set in and paresis; breathing, at first rapid, became appreciably slower. In half an hour he looked very ill, hunched up, fur ruffled, movement of nostrils spasmodic and slow; remained in one place, resistive to stimuli, shut eyes occasionally. Half an hour later hind-leg paresis had passed off, although still lethargic and disinclined to move.

Into No. 2 rabbit I injected intravenously the same amount of the same urine, but one-third saturated with anhydrous sodium carbonate. This injection had no apparent effect on the animal.

I had previously ascertained that 2 c.c. of normal urine had no effect on a rabbit when injected intravenously.

As regards treatment, in mild cases the indications are rest, warm clothing—in view of the fact that acidosis is nearly always associated with low blood-pressure; sleep, nutritious diet—avoiding fat, and including plenty of carbohydrates, Bynogen, Allenburys' diet, and such artificial foods; free purgation and alkaline medication. Potassium citrate is very useful, as, in addition to the fact that it changes into carbonate in the blood, it provides citric acid, which has the effect of restoring fat metabolism to normal, thereby reducing directly the acetonæmia. This, combined with the carbonates of calcium and lithium and the bicarbonate of soda, makes a very useful prescription. The more bases given the better. Free ventilation is necessary to secure an adequate supply of oxygen.

In a case showing more serious symptoms, complete rest in bed, and in addition to the above, enemata of 20 *per cent.* glucose solutions; while in a severe attack it may be necessary to give glucose or bicarbonate of soda intravenously. It might, indeed, be advantageous to consider gum-saline intravenously, as Bayliss suggested in wound-shock.

Glucose, it must be recollected, may behave as a weak acid in the blood.

Unless absolutely necessary for the provision of sleep, as little drugging as possible and as little disturbance in the way of chatter and interference—the exhausted and damaged neurone has quite enough to put up with. Be firm, and make the patient realise that his is a serious bodily disorder. In all but the mildest cases send the patient to hospital as soon as possible. The acetonuria having disappeared, continue a full dose of the alkali towards evening, and give a mixture of iron and arsenic. The experiments of Crile show that in these conditions strychnine is contra-indicated, as it caused cell changes precisely similar to those resulting from the emotions, toxins and foreign bodies, *viz.*, hyperchromatism succeeded by chromatolysis. With regard to means of control of the kinetic drive, Crile also states:

"Whatever the activation, whether infection, emotion, injury, or Graves's disease, morphine measurably controls the outward phenomena such as pulse-rate, respiratory exchange, sweating, thirst, restlessness, acid excretion, fever, muscular action and pain. . . ."

And it is interesting to note that so far back as 1822 De Quincy, in his *Confessions*, states opium to be—

". . . under an argument undeniably plausible alleged by myself, the sole known agent—not for curing when formed but for intercepting whilst likely to be formed—the great English scourge of pulmonary consumption . . ."

He considers that he himself was cured of phthisis between the ages of twenty-two and twenty-four by the regular and continued use of opium. There is at present here a patient, at one time a confirmed epileptic, who was given, many years ago, continuous and gradually increasing doses of opium for a number of years. During this period the fits disappeared, nor have they ever returned, though for a good many years now the opium habit has been broken off.

In conclusion, I wish to draw your attention to—

(1) The profound structural alteration in the neurone caused by acidosis and the extreme danger of permanent injury to it by continuance of the condition or by frequent attacks.

(2) The urgent need of early diagnosis, and the recognition that such cases are very ill indeed and need complete rest and proper treatment or they may become invalids for life and a burden on the community.

(3) The simplicity of the diagnosis.

(4) The fact that, as a rule, acidosis can be readily counteracted by efficient treatment.

(5) The need—in view of acidosis being a probable ætiological factor in epileptic states—for careful investigation, and the probability that, if such is the case, efficient alkaline treatment may cure the condition if recognised at the onset of the fits. The giving of bromides would seem to be dangerous in such a state, as it only tends to dull cellular activities. Later on it may be of use in treating nerve-cells which have acquired vicious habits.

(6) The danger to the patient in not adopting a firm attitude. If such cases are at once sent to hospital before serious mental symptoms come on there would soon be marked diminution in the admission-rate at asylums.

(7) The predisposition to microbic diseases afforded by acidosis, above all to tuberculosis. As regards children, there are questions which can best be answered perhaps by the general practitioner: for instance—What is the relationship between "biliousness" in children and subsequent tuberculosis? Are the sexes equally subject to acidosis? Does it throw any light on the greater mortality of male children? With regard to tuberculosis: Is it a question of the optimum reaction of the medium necessary for the growth of the tubercle bacillus? In other words, do certain individuals, as a result of errors of nutrition or faulty cell-metabolism, offer a more favourable pulmonary or lymphatic culture medium for the growth of the tubercle bacillus than do others?

Finally, is this whole question of acidosis, within limits, at the bottom of what we understand by heredity in respect to disease processes? Is it an effort on the part of the organism in some cases to autolyse itself? All these questions are of extraordinary interest, and the whole subject may bring us vastly nearer a proper comprehension of certain processes which up to the present have been shrouded in mystery.

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An Analysis of 200 Cases of Mental Defect.[1] By J. E. MIDDLEMISS, M.R.C.S.Eng., L.R.C.P.Lond., Medical Officer to the Leeds Committee for the Care of Mental Defectives; Late Assistant Medical Officer, Gartloch Mental Hospital, N.B.

THE cases dealt with in the present paper came under review during the course of my duties as Medical Officer to the Leeds Committee under the Mental Deficiency Act. They comprise examples of the four varieties of mental defectives defined by that Act, *viz.*, idiots, imbeciles, feeble-minded, and moral imbeciles, and include most of the clinical types described by writers on the subject. The commonly accepted

[1] A paper read at the Annual General Meeting, July 23rd, 1919.