and call the treatment "early," which was absurd. There was another failure to grasp what she was aiming at in the paper. Dr. Hyslop said that psychiatrists must not sling stones at neurologists, nor *vice-versâ*. She did not want to do that, but wanted the two departments to be so close together that they should be identical. All psychiatrists ought to be neurologists, and the neurologist ought also to be an alienist. Until they were all neuro-alienists the cases she had described would not be efficiently treated. Most of the speakers gave attention to the borderland cases which were certifiable and which required incipient care. They were not nearly so numerous a class, and hence were not so important. She was speaking of the extraordinary number of early nervous and mental cases which were not certifiable, cases which were avoided by the general practitioner who had had no training in mental cases, and avoided by the general hospital, which would not take them into the wards. She expressed, in conclusion, her lively gratitude for the interesting discussion.

(1) A paper read at the Quarterly Meeting, held in London, May 19th, 1914.

Epilepsy; A Theory of Causation Founded Upon the Clinical Manifestations and the Therapeutic and Pathological Data.(1) By J. J. M. SHAW, M.A., M.D.

The Manifestations of Epilepsy.

IN striking contrast to the elucidation of the cause and progress of various diseases by modern methods of examination, the phenomena of epilepsy, although long and widely studied, remain, to a very large extent, obscure. In recent years, however, some definite although dissociated facts have become known, and abiding views formed, from therapeutic and pathological data, and, within the last few years, from the investigation of the heredity of those afflicted. Although these facts may be comparatively few in number, it is surprising that no attempt is made even in the most recent text-book, to correlate such facts as are known and accepted, and to formulate a comprehensive theory which could be tested by experiment and further and independent observation.

The observed and verified features of the disease which require correlation are these:

The convulsive seizure, or "*grand mal*."

The minor attack, or "*petit mal*."

The occurrence in many cases of a warning, mental or sensory in character, of an impending convulsive attack, termed the aura; also the so-called "psychical" epileptic state of emotional instability and erratic conduct.

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The post convulsive states of stupor, sleep, or excitement.

The production of the epileptic phenomena and habit by trauma, gross cerebral lesion, and cardio-vascular degeneration (senile epilepsy).

The regular incidence of fits in many cases, especially during certain stages of sleep, and the occurrence in some cases of a fit at the inception of sleep, the pre-dormitial fit.

The strong hereditary factor in the disease, and its relation to various types of insanity.

The changes of a structural and biochemical type found after death in the cells of the cerebral cortex, and in the lymph spaces and capillaries.

The abnormalities of epileptic blood in regard to alkalinity, agglutinability, coagulability, and the formed elements.

The changes in relation to the convulsive state in the urine, especially its content of uric acid and phosphates, and the occurrence of post paroxysmal albuminuria and mucinuria.

The effects of various therapeutic substances, in particular the bromides and alkalies.

The benefits derived from the restriction of certain forms of food, and especially the purin bodies.

The Convulsive Seizure.

It is generally acknowledged that this state is produced by a sudden excitation and discharge of the cortical neurons.

"The function of the nervous system, and especially of the cortex of the brain, depends on a capacity for the instant release of nerve energy" (1). The regulation of the release of the energy is dependent upon an extremely delicate intermolecular action and transfer of the products of metabolism in true solution and in gaseous form between the cortical cells and the fine capillaries through the perivascular lymph spaces. The epileptic convulsion corresponds closely to the change produced experimentally by local mechanical stimulation, or by a sudden cerebral anæmia caused by obstruction of the flow of blood to the cerebral vessels, or by stasis or clotting of the blood in the capillaries and small veins. By occlusion of the carotid and vertebral arteries in a rabbit, Astley Cooper at once caused spasm, and the cessation of respiration (2).

Kussmaul and Tenner tied the left subclavian and innominate

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arteries of a rabbit. "The immediate symptoms were loss of consciousness and voluntary movement. These were followed in ten to forty-five seconds by clonic spasms beginning in the neck; then occurred dilatation of the pupils, respiratory gasps at longer and longer intervals, and finally cessation of respiration. After complete occlusion of these arteries for not longer than two to three minutes, the brain, on the ligatures being loosened, showed the power of complete recovery. The sudden re-entry of blood stopped the spasms, and in no case did it cause them" (3). Hill has produced clonic spasms in himself by compression of one carotid artery, and states that on sudden compression of both common carotids in man the pupils widen, respiration deepens, dizziness and loss of consciousness follow, and epileptiform spasms frequently occur (4).

A similar result follows the sudden cessation of the flow of blood due to local causes. The production of embolism by the injection of foreign bodies almost immediately causes cessation of the respiration, and rise of arterial pressure. Most important of all with reference to the *post-mortem* findings of Mott and Turner, to be later described, are the results of injection into the circulating blood of a quantity of thrombin solution (thrombin is a nucleo-proteid, according to Pekelharing and Huiskamp) (5) of leucocytes (which contain a large quantity of nucleo-proteid) and of tissue fibrinogen (6) (impure nucleo-proteid) all of which produce intravascular clotting; and also the experiments of Halliburton and Brodie (7). These last observers prepared a solution of nucleo-proteid of animal tissues such as the thyroid, thymus, and brain, by solution in *2 per cent.* sodium carbonate and distilled water. The injection of this solution into rabbits produced extensive and sudden intravascular clotting, and death when large injections were made.

"Respiration suddenly ceases, the animal makes a few stretching movements, and dies; there is no dyspnœa. Sometimes, after ceasing to breathe for about a minute, the animal gives a few breaths more, and sometimes resumes breathing normally." When a weak solution was injected in large amount salivation and muscular spasm were produced, the respiration ceased, and death ensued. An interesting idiosyncrasy towards the injection was evinced by Albino rabbits, in which even a very large amount of nucleo-proteid had no

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effect. The stoppage of respiration was due to the respiratory centres, section of the vagi having no result.

The Minor Attack.

In different individuals these attacks may vary from a slight and fleeting giddiness, which may pass unnoticed by the patient and his associates for a considerable time, to the more severe forms in which there is almost complete unconsciousness attended by slight muscular twitchings, by falling or some unusual or inexplicable action such as running forward suddenly and slowly raising the arms. It may be accepted that such phenomena differ only in degree from the major attacks in which a larger cortical area is involved.

Attacks of "petit mal" affecting the special senses are not uncommon, especially visual impressions, and these are referable to the corresponding tracts of the cortex in the same way as the purely psychical.

The Aura and "Psychical Equivalents."

Closely allied to the minor attacks are the sensory, motor, or psychical prodromata of the convulsion called the aura. They are in many cases a precisely similar manifestation, as was indicated by Herpin in 1857 (8), to the minor attacks, which may be considered as aborted or unspread seizures. A different train of symptoms is observable in some cases, and one patient in Bexley asylum at the time of his admission twelve years ago, when he had very infrequent fits, would inform the attendants of a slight feeling of *malaise* almost a month before an attack. This sensation gradually developed into a headache as the day approached on which the fit was about to occur, and quarter of an hour before the convulsion actually took place he would leave his work in the ward kitchen and carefully lie down on a couch, loosening his necktie and collar. With an increase in the number of attacks and growing dementia, he has lost the ability to forecast his fits with any degree of accuracy.

Another patient feels a pain at the vertex for several days before an attack, and, as his fits are almost entirely related to the inception of sleep, he sits up in bed for many hours to apply

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the sensory stimulus which grasping one arm tightly by the other hand produces. A strong hypnotic (Chloral hydrat. gr. xx., pot. bromid. gr. xxx, in one dose) which the patient frequently asks for, is often efficacious in producing sleep without the occurrence of a seizure.

I believe that many of the familiar epileptic traits of impulsiveness, violence, and vicious actions may have a physical explanation in the loss of sense of well-being, and so are in reality the outcome of an "irritability of weakness" in patients who do not recognise in them the long drawn out warning of a convulsion.

The Post Paroxysmal States.

In several cases I have produced a marked abbreviation of the post convulsive state by the exhibition of ammonium oxalate and oxalic acid in very small doses, which I shall later describe.

Traumatic Epilepsy.

Following severe injury to the cortex, and in some rare cases cranial injury without gross brain lesion, convulsions may occur which bear an exact resemblance to the so-called idiopathic type. In many such cases a slight focal softening is present which affects the nutrition of the surrounding areas by derangement of the fine capillary network. In the same way a tumour will cause local vascular change in addition to a general increase of pressure. "The growth of a tumour within the cranium may produce compression of the cerebral capillaries. The cranial contents cannot be increased and if the quantitative ratio of cell tissue to blood vessels be altered it must be at the expense of the blood volume" (9). Senile thickening and irregularity of the vessel walls similarly tend to impair the uniformity of the blood-supply from arteries to arterioles, and from arterioles to capillaries, and so magnify the effect of a slight anæmia of postural or cardiac origin.

The Time Incidence of Convulsions.

Many exhaustive analyses of the incidence of the major and minor attacks have been made by different observers, and these correspond closely when the average of a large series of cases is taken.

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The Hereditary Factor.

In appendix A will be found the hereditary tables of six cases from the records of Bexley asylum.

Cerebral Pathology.

Although many cellular degenerations and local scleroses have been described, there are very few changes in the cortex or basal ganglia which can definitely be delimited as epileptic. Similar changes may be found, on the one hand, in the brain of all patients subject to sudden and recurring seizures, such as general paralysis of the insane, and, on the other, in the subjects of imbecility with which epilepsy is often associated. The vacuolations of the nuclei in the cells of the second cortical layer, which was described by Bevan Lewis (10), and upon which he laid much stress, has been shown to be an inconstant feature in epilepsy, and also to exist in other conditions such as tuberculosis and pneumonia (11).

Disappearance of the intra-nuclear reticulum and its replacement by a fine, irregular, granular deposit has been described by two American observers (12) and confirmed by Turner (13), by whom a large number of important changes have recently been described. Turner considers that this granular change is preceded by an enormous bladder-like distension of the nucleus forming the acute stage. He has found a similar condition in the cortex of a dog after ligature of the cerebral arteries, and holds it as evidence of the occurrence in epilepsy of sudden stasis in the cerebral capillaries.

The deepest layer of the cortex, which shows a yellowish-red appearance on fresh section, indicative of a slightly greater vascularity than that of the strata external to it, is sometimes termed the polymorphic layer. The cells are rich in nucleoproteid, and in this layer, and the small pyramidal layer immediately superjacent, the dendritic processes are believed to be actively amœboid. The perivascular lymphatic spaces are comparatively large, and the cells are freely bathed in lymph. In a case of organic dementia in Bexley asylum in which the seizure closely simulated those of epilepsy in the nature of the spasm, remission by clonus, extreme cyanosis, and rapid recovery, a narrow, irregular stratum of reddish-yellow and yellow softening was found *post-mortem*, involving only the

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deepest cortical layers, and, to a slight extent, the underlying white matter in small areas. The cortical layers external to the line of Baillarger presented the usual greyish colour. These lesions were found in the right motor and left frontal area.

A similar narrow strip of advanced softening was found in another case with sudden convulsions, but in this brain there were also softenings in the right corpus striatum. The blood-vessels of the cortex, which arise from those of the investing pia mater, run more transversely in the inner than in the outer cortical layers. The lymph spaces are formed chiefly of fine processes of pial membrane, and the usual trabeculæ visible in the other regions are not seen in the cortex.

Sclerosis of the hippocampus major, which is commonly found in epilepsy, has been thoroughly investigated and described at great length. It is not now considered as a causative factor (14), and Turner attributes it to occlusion of the nutrient vessels.

Mott has demonstrated micro-chemically that biochemical changes occur in the cortical neurons at temperatures of 105° F. and 106° F., and also after epileptic fits, even without pyrexia. He states that the observed changes are due not to exhaustion, but to an altered chemical condition of the lymph in which the cells are bathed (15). He further states that the congestion and stasis of the vessels along with œdema of the brain, inasmuch as it is contained in a closed cavity, must be associated with a corresponding arterio-capillary anæmia (16).

The changes in the pia-arachnoid membrane do not call for detailed description. The most important observations are those of Turner, who has found in the lesser vessels of the membranes changes similar to those in the cortex (17).

There is no marked thickening of the walls of the smaller cortical vessels. The lymphatic perivascular spaces are dilated. Sir James Barr (18) states that the size of the capillaries of the body varies between 7 to 13 micromillimetres. In the cortex, although Ford Robertson gives 4 micros. as the minimum of fineness, Turner states positively that he has found capillaries of from 1 to 2 micros., in passing through which the erythrocytes become elongated (19).

Several observers, including Osler, have shown that blood plates in aggregated masses cannot pass through capillaries. Turner finds many indications that stasis in the smaller vessels

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is produced in a great degree in epilepsy, and to this condition, suddenly effected, he attributes the rapid anæmia which results in a convulsion. The general congestion which is recorded by all observers is due to engorgement of the capillaries and small veins, the arterioles being comparatively empty. Associated with the congestion, Turner has observed numerous petechial hæmorrhages scattered throughout the cortex, and small angiomata have been observed (20). Turner attributes the dilatation of the capillaries in status epilepticus to a compensatory rise of blood-pressure to overcome the distal blocking by masses of the formed elements. Spheres composed of agglutinated blood-plates (containing phosphorus and thus indicating their nucleo-proteid origin) are found lying in the capillaries, also hyaline casts due to a complete fusion of the platelets, granulated *débris*, and rarely threads of fibrin.

I have found, and will later describe a tendency in the blood of epileptics to abnormally rapid agglutination, with comparative slowness in the formation of a true retractile clot, and this is in harmony with these *post-mortem* observations.

A condition which Turner emphasises is the presence of a frothy exudate in the sub-pial space, which, he states, also exists in the communicating perivascular spaces. In almost all the cases of general paralysis in which there has not been actual adherence of the membranes to the brain, I have found a similar sticky exudation. It is most commonly found in rapid cases, and in those in whom seizures have been absent or infrequent, and I regard it as the first stage in the adherence of the membranes. Combined with a granular wasted appearance of the summit of the convolutions, I have also observed it in three epileptic brains.

Contradictory observations have been made upon the composition of cerebro-spinal fluid, especially as to the presence of cholin. It may be accepted that there is no pronounced deviation in composition from other congestive seizures and states. Cholesterin is commonly found, and the important observation has been recently made that the carbonates, uric acid, and lactic acid may also be present (21).

The Blood in Epilepsy.

In recent years the physical and chemical abnormalities of the blood have been the objects of much research. The

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conditions which I shall describe at present, like the other matters treated in this section, are intended to take a place in the large series of premises from which a conclusion can later be drawn.

The reaction of healthy blood is very slightly alkaline, and that of the serum, when the alkali protein compounds in the formed elements are eliminated, is practically neutral (22).

The blood corpuscles give up a part of this alkali united with protein to the serum by the action of carbon dioxide, hence the serum becomes more alkaline (23). The addition of carbon dioxide of course decreases the total alkalinity.

The alkalinity changes transitorily after absorption of some foods, and may be altered by the exhibition of acids and alkalis. It presents, however, a regular diurnal variation, being low in the morning, high throughout the day, and falling again in the evening (24). The total reaction may become actually acid in cases of uræmia, diabetes, and cholera (25) (26). In one case of diabetes the amount of acid per kilometre was equivalent to 1·75 grammes of H.Cl. These changes imply a considerable degree of acidity of the serum.

The researches of Charon and Briche (27) upon the reaction of epileptic blood showed that the seizures occurred in inverse relationship to the degree of alkalinity, the minimum frequency of the attacks corresponding to the maximum blood alkalinity, and *vice versâ*. The conclusions of Pugh (28) in relation to the final issue of this thesis are of sufficient importance to be quoted in full :

"The average alkalinity of the blood in the interparoxysmal states is lower than the average of the control cases.

"The diminution is gradual and progressive, and is more marked in cases suffering from gastric catarrh and constipation. There is marked sudden and pronounced fall immediately prior to the onset of a fit.

"There is a further fall in alkalinity after the fit is over ; this diminution is seen in from three to ten minutes after the attack.

"This after-diminution depends on the duration and severity of the muscular twitching, and upon the degree of interparoxysmal alkalinity.

"There is a gradual return of the blood to its normal alkalinity, which takes place in five to six hours, the rise being more marked in the first hour.

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" If the alkalinity keeps at a low level it may determine the onset of another fit.

" The diminution after the fit is due to the chemical end products of muscular metabolism, *i. e.*, sarcolactic and carbonic acids, and not to substances in direct relation to epilepsy.

" The diminution after the nocturnal fit takes a longer time to return to the normal than the diminution after a day fit."

Pugh finds that the administration of bromide salts at first raises the alkalinity, but this is not maintained even with increased dosage, thus indicating that the bromides must have another means of controlling the convulsive states than by merely affecting the alkalinity.

The metabolism of the tissues depends upon a certain degree of alkalinity of the circulating fluids, and it is essential for the activity of the cortical neurons. As a result of metabolism acid products accumulate, among which are lactic, carbonic and uric acid, and urea. Uric acid is derived from katabolism of nucleo-proteins. It is found along with the purin bases choline and paralactic acid as an extractive body in the normal brain (29).

The viscosity of the blood is dependent upon two factors: the number of the formed elements and the quotient of the carbon dioxide, being high when the corpuscules are increased and when the blood is rich in carbon dioxide (30).

The viscosity increases during narcosis according to the depth of the sleep (31).

The increase in viscosity is a stage in the development of agglutination and coagulability, and viscosity increases in degree according to the reduction in the alkalinity. Dastre and Floresco (32) have found that non-coagulable peptone plasma is alkaline, and that it loses its non-coagulability if rendered neutral or faintly acid. Emerson finds that the alkalinity rapidly diminishes till coagulation is effected, and then it remains almost constant (33).

As an intermediate stage between the highly viscous but still fluid blood and coagulation with the formation of a retractile clot and exudation of serum comes agglutination. The mechanism of agglutination, which is probably of greater importance clinically in the development of stasis and thrombosis than coagulation, has been only partially studied, although its importance was recognised by Hunter in 1873. It may

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occur in defibrinated blood and is not dependent on fibrin formation. Addis (34) finds that the first appearance of slight stasis is too rapid and variable a feature in a suspended drop of blood to be taken as a determining point in the estimation of coagulation. Such a stasis, however, would be of the greatest importance in the network of capillaries, especially in the cortex. It is probably due to a simple cohesion of the corpuscles in the presence of the highly viscous blood plates before and during their interaction with prothrombin to form thrombin, which eventually acts upon fibrinogen transforming it into fibrin.

In relation to the discoveries of MacCallum and Voegtlin (35), regarding the calcium content of the blood in experimental tetany, I made preparations to estimate the calcium content of the blood in epileptics by Wright's method (36).

This consists of the estimation in a long and fine capillary tube, of the concentration of ammonium oxalate which permits, and that which inhibits coagulation in a series of dilutions, and so the quantity of calcium in parts per 1000 of blood. After some practice the method worked easily and well, and I obtained uniform results, using my own blood and that of six non-epileptic patients whom I intended to use as controls. In none of these instances was there the slightest difficulty in intermixing the drops of blood with the dilutant on a glass slide, and drawing them up into the long capillary tube. I then proceeded with the same apparatus and solutions to apply the method to my epileptic cases, but was surprised on the first day to find that only five out of the thirty-two dilutions in the four cases would enter the tube, agglutination having taken place almost immediately. On continuing these investigations upon my other cases (*vide* Appendix B), I found the same phenomena in nearly every instance, which rendered the method entirely inapplicable to epileptic blood, so far as the calcium content was concerned, but was extremely interesting as regards the agglutinability. A much deeper stab was required to produce a sufficiency of blood in the epileptic than in the non-epileptic cases, and the flow ceased very quickly, I believe the abnormality to be due partly to an excessive and readily accessible quantum of thrombokinase in the injured tissue cells of the wound, and to a ready disruption of the polymorph leucocytes, and liberation of the thrombokinase

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content of the blood plates. I attempted to estimate the comparative times of agglutination in different cases by placing a series of drops on a slide, and taking the earliest time at which a drop could not be drawn into the capillary tube at the point. As the differences were, however, matters of seconds, and depended largely upon the rate of flow from the wound, I could not get reliable or constant results, or estimate the relation to convulsions; but I attached great importance to the general greatly increased rapidity in agglutination in epileptic compared with non-epileptic blood.

In contrast to this rapid agglutination, I found the formation of a true retractile clot very rare in those specimens of blood, even when mixed with the weakest dilutions of ammonium oxalate, which did enter the tube. A simple sedimentation and cohesion of the corpuscles occurred which on expression into water failed to maintain the thread-like shape of a clot, but broke up in granules, or disseminated in a fine pinkish cloud.

In the presence of the chlorides of sodium, and more strongly of calcium, a true clot with exudation of serum between the thread of clot and the walls of the tube was visible, and this maintained its form when expressed into water, like a clot from normal blood undiluted or in the low dilution of oxalate.

It is highly probable that this rapid agglutination may have vitiated the results of observers who have removed the blood direct from the wound into capillary tubes, and who have found the "coagulation" time unusually rapid in epilepsy; so far as I am aware, the coagulation time in epilepsy has not been estimated by the recently devised oil-impingement method of Addis. Addis described a similar sedimentation and agglutination in the majority of bacterial diseases, typhoid being a marked exception, and in uræmia, acute nephritis, and cirrhosis of the liver, and quotes the opinion of Flexner that this agglutination may be a source of thrombosis in disease (37).

Turner found a considerably reduced coagulation time in the periods immediately before and after the convulsive attacks, as well as a general reduction in the interparoxysmal periods (38). These results, in view of the relation which has been mentioned between reduced alkalinity and coagulability, are in accord with Pugh's observations upon the reaction of the blood in epilepsy.

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The Cellular Elements.

No pronounced change has been observed in the number or character of the erythrocytes in epilepsy, but numerous variations in the leucocytes have been recorded. Contradictory statements have been made regarding the total leucocyte count. Lewis Bruce finds a persistent hyperleucocytosis more marked after the paroxysmal periods, when it may rise to 30,000, a result which he attributes to toxæmia (39).

J. Turner states that a considerable leucocytosis is usually present, but has not observed any marked variation in the paroxysmal period (40). McPhail found a leucopenia of 20 *per cent.* below normal, which altered to normal on the administration of the bromides (41).

Pugh (42) has found a constant increase in the leucocyte count after convulsion, the increase being due to the small and, to a less extent, the large hyaline cells. The polymorphonuclear cells are diminished. The degree of leucocytosis is not so marked in status epilepticus, and is diminished with each seizure.

My own observations (Appendix C) conform to those of Pugh in the differential counts, but the total numerical variations before and after seizures were not greatly marked. I also failed to find what could be called a hyperleucocytosis in any case in the interparoxysmal period, the maximum of twenty-eight cases being 15,800, the minimum 7,600, and the average between 10,500 and 11,000.

The blood-changes at the convulsive periods are of great interest, like the hypo-alkalinity, in relation to the hypothesis of cortical endovascular stasis and agglutination.

According to the views of Schmidt and the Dorpat school (43), an abundant destruction of leucocytes, especially polymorph, takes place on coagulation. I have examined on several occasions agglutinated blood by compressing it between cover slips and staining, and also the soft agglutinated masses of corpuscles which form the so-called *post-mortem* clot. In both conditions, although the leucocytes have lost their affinity for basic dyes to some extent, I have found a comparative diminution in the number of polymorph cells. Some investigators believe that there is no actual disintegration of the

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polynuclear cells on coagulation, but merely an elimination of their constituents, a process called "plasmoschisis" by Lowit.

The blood-plates, with which I shall deal later as an important nucleo-proteid-containing element, are said to be considerably increased in the blood after convulsions, and have been found in agglutinated masses in the cerebral capillaries (44).

In cases of chlorosis in which the blood plates are increased in number it is said that a special tendency to venous thrombosis exists, and in some of these cases long, cylindrical masses of plates, which probably have been washed from the capillaries, can be found in the film (48).

The gaseous changes in the blood in epilepsy have not been greatly studied, but it has been found (45) that in epileptiform fits, provoked in animals by injection of the essential oil of absinthe, a much greater increase in the carbon dioxide content of the blood takes place in the torcular herophili than in the femoral veins and carotid artery.

The Urine.

Closely allied to the variations in the reaction of the blood are the changes in the uric acid output in the urine. A diminution in the quantity of the uric acid in the urine passed before a convulsion and an increase in the first quantity passed after it, has generally been observed (46) and examinations which I have made confirm this observation. This change is not observable to the same degree after minor attacks. I have also found an almost constant albumosuria in the post paroxysmal urines and a constant mucinuria (*vide* Appendix D).

The presence of toxins in the urine has been the subject of exhaustive researches with contradictory results (47).

The occurrence of albumosuria is of especial interest in relation to the comparative reduction of the polynuclear cells in the post paroxysmal blood.

I have found a slight increase in the phosphate secretion after convulsions (Appendix E).

Results of Treatment.

The medicinal treatment of epilepsy has come to be associated almost entirely with the bromides since their introduction by

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Sir Charles Locock in 1857. They have been universally recognised as the most potent group in controlling the convulsive attacks, and in many instances have been accepted as the means of cure in patients who have ceased to have fits after the exhibition of bromides for long periods.

To take the diminution of the actual convulsive attacks as the sole criterion of treatment is, however, becoming increasingly discredited. That bromides may have a depressing effect and may produce serious symptoms in those who require more than a small dose is well recognised. I have found that many patients prefer even a considerable number of fits along with a proper sense of well-being in the intervals to the bromide effects of impaired appetite and lessened mental and physical efficiency; but one must remember that the serious contingencies of convulsions are obviated to a great extent in institutions by appropriate work and play, and by continuous observation of cases who may be injured by a sudden fall. Belladonna, an old remedy, is still used, and digitalis is a useful adjunct to treatment.

The alkalies, especially biborate and carbonate of soda, have been proved to be useful, and I found in several cases great improvement resulting from the latter.

From the exhibition of oxalic acid and ammonium oxalate in $\frac{1}{2}$-gr. and grain doses respectively, I have received most gratifying results in certain cases. In several instances I have observed a marked diminution in the number of convulsive attacks and a great diminution in the attacks of *petit mal*. While they are less effective in controlling the major attacks, in the small doses in which I gave them, than the optimum dose of bromide, I believe that they are more effective in diminishing the minor attacks. In some cases I gave oxalic acid gr. j before breakfast, and 10 or 15 gr. of ammonium bromide at bedtime with very good results. But more important than its action upon convulsive attacks has been its effect upon the patient's mental condition and the curtailment of the post-seizural depression and confusion. One case, who had been on bromide almost continuously since his admission (except in the control state in which he had no medicine) twelve years ago, and was regularly known to exhibit a post-seizural phase of stupor followed by restlessness and impulsiveness lasting from one to four hours followed by headache, this

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patient after his first fit, four days from the inception of the oxalic treatment, rose about four minutes after the cessation of clonus, walked unaided to the ward from the bath-room, where he was at the time of the fit, and commenced his work in the boot-room. This marked curtailment of the post-paroxysmal state has been evident now without exception for seven weeks.

To avoid obscuration of the central idea of this thesis, I have placed the details of my oxalic treatment and of the other substances which I used in Appendix F.

I will only mention in this place that from the exhibition of the glycerophosphates, including calcium glycerophosphate, phytin liquidum, and Sanatogen, I obtained deleterious effects, both the frequency and the severity of the fits being increased.

I obtained no pronounced effects from the exhibition of emulsion of lecithin or from the calcium salts, but such as were produced were bad. Calcium bromide I consider to be inferior to the other bromide salts in common use.

Dietetic Treatment.

A salt-free diet, first recommended by Hughlings Jackson, has been widely tried and has been found a useful adjunct to the administration of bromides. A great success has been claimed for it at the Massachusetts Hospital (49). In three out of four cases in which I added ʒij of salt daily to their usual quantum no effect was produced. In the fourth case a marked increase in the number of fits occurred, and he exhibited a marked diuresis, passing on one occasion 130 oz. of urine in twelve hours. This fact is interesting in view of the statement of Straub and Rost (50), that if the increased ingestion of salt be accompanied by diuresis, which is not compensated by drinking water, a rise in the protein metabolism occurs.

Operative interference has not produced good results in many cases. It has recently been recommended by Dr. Alexander who at the Maghull Institution has observed benefit by an operation, the object of which is the drainage of the sub pial space by puncture of the soft membranes and fenestration of the dura mater (51). In these cases he has found an excessive œdema of the pia arachnoid membranes, and excess of sub pial fluid, which is clear, sterile, and of the constitution of dilute lymph.

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Theories of Epilepsy.

Three propositions which have been advanced to explain the phenomena of the disease, but do not appear to me to come within the category of accepted or proven fact, require mention and elimination. They are:

The microbic origin.

The purely toxic.

The cardio-vascular theory supported especially by Dr. A. E. Russell.

Dr. H. M. Greene of Portland, Oregon (52), states that he has observed the presence of a large diplo-, and small micrococcus in two specimens of the blood of a case of epilepsy following scarlet fever, and also in another idiopathic case without a known toxic or febrile origin. He reports that he managed to prepare a valent vaccine from these bloods, but further observations during twenty years have failed to support his findings.

The presence of an organism which he called the "neurococcus" has also been described by Bra, and discredited by other observers who showed it to be the creation of faulty technique (53).

That a large number of cases date their origin from an attack of scarlet fever has been generally approved (54). Gowers emphasises the fact that the toxins of the disease give rise to chemical changes in the nervous system, as shown by the frequent occurrence of optic neuritis as a sequela. Influenza has a similar but less marked effect in provoking epilepsy. The speculation that deleterious effects may be produced in some cases of scarlet fever in the eliminatory cells of the choroid plexus comparable to the changes in the renal epithelium is instructive, and may account for the morbid changes in the cerebro-spinal fluid in such cases.

Inclusion bodies in the polynuclear leucocytes, of similar appearance and reaction to some which I will later describe, have recently been observed in excess in scarlet fever (55).

A microbic condition is not in accordance with the nature of the disease. It bears no relation to successful although admittedly empirical treatment, and it receives mention but no support in modern literature.

Although various toxic substances, especially cholin (several observers), and carbonic acid (Krainsky), have been ascribed as

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the direct cause of convulsions, their actual causative nature has been found experimentally defective, and the strong balance of opinion places them as a resultant and not a provocative change in relation to the paroxysms.

A large mass of evidence has been adduced by Sir A. E. Russell in support of the theory of causation by cardio-vascular insufficiency and, in a much less conclusive way, by arterial spasms in the cerebrum.

He maintains (56) that the difference between faint and epileptic attack is a difference in the degree, and not the kind of cerebral anæmia, and difference in rate of development. "In the ordinary faint the cerebral circulation slowly diminishes *pari passu* with the falling blood pressure. In the fit there is sudden cessation of the circulation. In the faint the circulation slowly improves; in the fit it returns with greater rapidity." Stress is laid on the fact that loss of consciousness may precede convulsions (57). He quotes three cases of Gowers' in which syncopal attacks in childhood have passed into epileptic attacks in adult life, and also three of Moxon's in which epileptiform attacks followed an arrest of the heart's action which he attributed to vagal inhibition. Russell states that the pulse irregularities are great, and the vaso-motor system unstable in epileptics.

While readily accepting the statements that a sudden cerebral anæmia produced by cardiac or vaso-motor change may be the cause of epileptiform attacks, as best shown in the phenomena of the Stokes-Adams syndrome, in which brady-cardia and arhythmia are always present, the evidence that this is the usual, or even a rare, cause of idiopathic epilepsy is wholly insufficient. Even admitting that a vaso-motor or cardiac instability is present in some cases, Russell fails to show, except by analogy with the Stokes-Adams syndrome, where an extreme circulatory disorder obtains, any form of sudden excitant of the attacks.

In the discussion which followed a lecture by Russell on the Pathology of Epilepsy (58), in which he maintained the cardio-vascular theory, the *post-mortem* results of Leser were adduced in opposition to Russell's arguments. Leser found in 500 epileptics that 1½ *per cent.* had signs of heart disease, and in 800 diseased hearts not 1 *per cent.* were epileptic. Aldren Turner (59) has found valvular disease of the heart in 1·8 *per cent.* of his cases.

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The results of three observers in a number of cases show that there is no considerable change in the rate of amplitude of the pulse until the clonic state is reached, and no sudden lowering of blood pressure occurs. They agree that the cause must be a local one in the brain rather than a sudden fall in pressure from cardiac inhibition or splanchnic dilatation (60).

The fact that the pulse rate may be slightly reduced, and may occasionally become irregular when satisfactorily felt in the clonic spasm is of little importance if we consider the degree of muscular pressure which is exerted upon the blood vessels during a convulsion. As a rule the frequency and force increase at this stage (61). In examination of the fundus oculi by the direct method from before the commencement of the fit to the end, Gowers has not detected in several cases the slightest change in the size of the vessels (62). This serves to contradict the purely speculative theory of arterial spasm, and, indeed, the presence of vaso-motor nerves in the walls of the cerebral vessels has not yet been conclusively demonstrated (63) (64).

With a view to determining the degree of the alleged vaso-motor instability in epileptics I have made fairly comprehensive observations upon the pulse mobility, the blood pressure, *tache cérébrale*, capillary pulsation, the state of the heart and vessels, and the soundness of sleep in epileptic and non-epileptic cases. (Appendix G). The total result is to show a very slightly greater degree of instability among epileptics, chiefly in the senile cases, but one quite insufficient in my opinion to be a causal factor in the disease. Following a major attack the instability, in company with that of other functions of the body, is naturally greater. The cases which I took were all upon the same dietary, and were in bed for exactly the same number of hours per night. The general state of sleep among epileptics appeared to be deeper than in non-epileptics.

Between the foregoing critical analysis of the conditions which obtain in epilepsy and the second part of this thesis, in which I shall endeavour to substantiate a correlating theory of causation, I will, for the sake of clearness, interpose a brief statement of the conditions which I believe to be responsible for the epileptic manifestations.

The convulsive and minor attacks in epilepsy are produced by a sudden cerebral anæmia due to a stasis of the circulation

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in the cerebral capillaries and small veins which is removed at once, or by degrees, by the rise of the blood pressure and increased pulse-rate which occur when stasis has been effected. The actual convulsion may be preceded by an aura due to increasing viscosity, and a rapidly developing stasis of the formed elements of the blood, and may be succeeded by a period of irregular cortical excitation as the agglutinated elements are removed from the fine capillaries, and the cells again become oxygenated. The frequent occurrence of this paroxysmal state is the explanation of the *post-mortem* findings of Turner, Mott, and others. The stasis is produced by a quantitative change in all the nucleo-proteid elements of the cells in epileptics, nucleo-protein forming the largest moiety of the cells of the affected layers of the cortex, of the agglutinating elements of the blood, the blood plates, and of the polymorph leucocytes whose disintegration favours agglutination and coagulation, and which are found to be diminished in number after convulsions. This disintegration is the explanation of the katabolic elements found in the post convulsive urine.

The nucleo-proteins exist in a soluble and precipitated state in the body, and the change in these states, in the circulating media, is dependent upon a minute change in the acidification of their solvent, or upon contact with a foreign body. This change has been demonstrated in the fall in alkalinity prior to a convulsion, and the general incidence of the attacks in relation to the alkalinity of the blood.

The assimilation of nucleo-protein increases the element favouring coagulation in the blood. The assimilation of the components of nucleo-proteid in the purin bodies and the glycerophosphates has a similar effect.

The bromides have a special affinity for nucleo-proteins and retard their metabolism.

Nucleo-protein.

In all standard classifications the nucleo-proteids are grouped as conjugated proteins along with the gluco- and chromo-proteins (65).

They are compound proteins which are characterised by yielding protein and nucleic acid on cleavage. They are present in large amount in the cells of the body, especially the brain, in

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which they are found in greater amount than any other protein (66), and are particularly abundant in the polymorphonuclear leucocytes (67). They are insoluble in water, except in the presence of alkali, and from such a solution which, if concentrated, is slightly viscous, they can be precipitated by weak acetic acid, forming an amorphous white deposit. The degree of alkalinity required is extremely small, and I have found in many cases the change from solution to precipitation in ten cubic centimetres of the fluid to be dependent upon the addition of one minim of 1 *per cent.* acetic acid. A similar proclivity to complete change of physical state by minute change in the reaction of the solvent is exhibited in resolution, especially in freshly prepared solutions.

They are resembled by the phospho-proteins in that they contain phosphorus, and have the same properties of solubility, but differ in respect that the nucleo-proteins yield purin bases on cleavage, while the phospho-proteins and lecithalbumins (which are also allied, but differ in solubility) do not. The mucins exhibit a similar solubility, but contain no phosphorus. In the nucleo-proteins the phosphorus is contained in what Kossel (68) calls the "prosthetic" group, or side chain, consisting of nucleic acid, which can be split off from the protein, whereas in phospho-protein a simple salt-like formation obtains between the phosphorus containing moiety and the proteins.

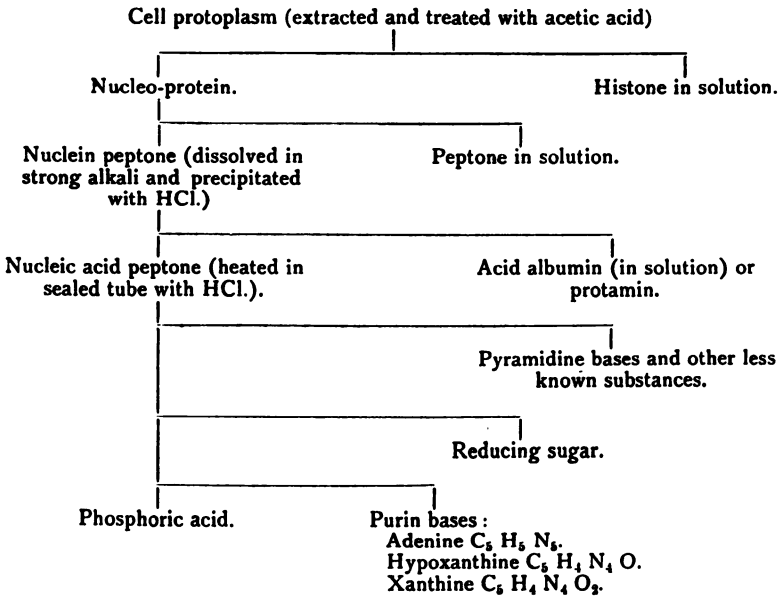
The brain also contains a large number of other phosphorus-containing substances of the cerebroside class, and protagon which Cramer considers to be an integral substance: also the ether-soluble lipoids, of which the chief is lecithin, which also contains phosphorus.

The variations and interactions of these substances are extremely rapid and complicated, and can only be partially reproduced *in vitro*.

As the nucleo-proteins occur in the cells they are in most cases soluble in water or salt solution, which is comparable to the lymph, but after separation they need the presence of a small quantity of free alkali for their solution (69). When freshly prepared from protoplasm they are highly unstable, and undergo changes in repeated precipitations and resolutions.

The disintegration of nucleo-proteins may be carried out *in vitro* as follows (70):

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Uric acid ($C_5 H_4 N_4 O_3$) is also a purin, although its exact relation to the other bases and to cellular metabolism has not yet been fully demonstrated. It is probable that part of the basic residue of nucleo-proteins may undergo oxidation in the body and appear in the urine as uric acid, while another part may escape oxidation and appear as the so-called alloxuric bases (71).

A solution of nucleo-proteid can be obtained from many of the tissues, and in considerable quantity from the brain. In Appendix H, I have stated the results of a series of quantitative estimations of nucleo-proteid and other soluble substances from brains of various forms of insanity. The brain substance is finely macerated, and placed in an aqueous solution of sodium carbonate (1·5 *per cent.*) for twenty-four hours. It is then filtered, and the nucleo-protein precipitated by the addition of 1 *per cent.* acetic acid. The supernatant fluid is removed, and the precipitate dissolved in ·5 *per cent.* sodium hydroxide. The quantitative results which I have obtained do not show any marked variation in the cases of epilepsy from other brains, and in my opinion the quantitative differences are due probably not to the form of insanity, but to personal variations ; possibly

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the mode of death in different cases, slow or rapid, seizural or non-seizural, may have some influence.

All brains were placed in the first solution within thirty-six hours after death.

There were wide individual differences in the behaviour of the solutions in precipitation and resolution. Treated in exactly the same manner the solutions were all slightly viscous, but some were translucent, and others markedly opalescent. The great majority of the solutions became suddenly turbid when the adequate quantity of acetic acid had been added, and the amorphous nature of the precipitate was observable within half a minute although it settled slowly in the long graduated tubes which I used. In other cases, although the opacity increased suddenly, the aggregation of the particles to form the amorphous precipitate did not occur until an hour after the acid had been added.

In one case, from an imbecile brain, while the opacity was increased by the addition of acid no precipitate appeared in twenty-four hours, but I then obtained a small precipitate containing a minute trace of phosphorus by adding 15 minims of 10 *per cent.* nitric acid to the 30 c.c. of solution. I estimated the phosphorus contents in the thirty-seven samples of nucleo-proteid, and thirty-one of the lipoids, and found that it bore a fairly constant ratio to the amount of the precipitate.

In two samples which were prepared with half the usual amount of sodium carbonate solution to the same quantity of brain substance I obtained, by carefully adding the weak acid to the alkali solution in a series of test-tubes, a precipitate when the reaction was neutral to the sensitive litmus of Kubel and Tieman, but in five other similar concentrated solutions which I tried no precipitate appeared until the solution turned acid.

The precipitated nucleo-proteid has a ready affinity for basic dyes. In two specimens, which I allowed to stand for over a week in the precipitated state, I found when examined microscopically a few well-marked crystalline rosettes, exactly resembling the crystals of uracil, a pyramidine body, among the *débris*, but the majority of stale precipitates showed no such change.

I found that the addition of various salts produced a similar phosphorus-containing precipitate to that of acetic acid, those

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most rapid in effect being calcium and sodium chloride, and magnesium sulphate. The addition of saturated calcium chloride to a quantity of macerated brain produced a thick coagulum which lay at the top of the solution. In some cases this reaction was so rapid that, using test-tubes of an inch diameter, the whole tube would be inverted without the fluid flowing past the coagulum within half an hour. No other salt produced such a rapid effect as calcium in this way. This effect could not be produced upon the residue left after the nucleo-proteid extraction by sodium carbonate, and I surmise that calcium, which is always found in brain substances, has a special coagulative effect in strong solution upon the unaltered nucleo-proteid elements, although it produced a simple precipitate and not a coagulum from the alkaline solutions.

In addition to the nucleo-proteid elements of the cells of the brain, the following substances can be found: the purin bases, paralactic acid, phosphocarnic acid, and uric acid. Metabolism is always most rapid and complete when the fluid which bathes the cells is alkaline. The process of metabolism causes the accumulation of acid substances which are disintegration products. This accumulation gradually prevents or diminishes the degree of further change, and so the equilibrium of body metabolism and that of the cortex is maintained. I have already referred to the extreme fineness of the cortical capillaries, and to the comparatively large perivascular lymph system by which the interchange of substances between blood and tissue cells is rapidly effected.

The Action of the Halogens upon Proteins.

The relation between chlorine, bromine, and iodine and the proteins has only received any considerable degree of attention in recent years, although as long ago as 1848 Mulder obtained a precipitate which he called "protein chlorous acid" when chlorine was passed into a solution of egg-albumin. The method which is now chiefly used (72) is the passage of a stream of chlorine or bromine through a weakly alkaline solution of protein. Blum and Vaubel found that it was only in an alkaline solution that the maximum halogen-protein combination could be obtained. "A definite series of bromine derivative was obtained from proteids, each with a constant

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amount of bromine, by varying the methods of preparation. It was not found possible to obtain such a definite series with either the chlorine or iodine preparations."

The precipitate formed is soluble in 1 *per cent.* sodium hydroxide, and suddenly reprecipitated by addition of a slight excess of weak acetic acid.

It is interesting to observe the exact similarity in the solubility of these compounds and that of the nucleo-proteins, especially in view of the fact that both the substances used in these investigations, caseinogen and ovalbumin, contain phosphorus in protein combination in considerable quantity.

From my own observations I believe that the halogen affinity is greater in the case of the phosphorus containing proteins, and especially the nucleoprotein, than in any other group.

I have observed the effect of bromination upon a considerable number of solutions of nucleo-protein obtained from brain, and find that in bulk and weight the bromine precipitate was usually slightly larger than that obtained by precipitation by acetic acid. The bromine solution was prepared by slightly heating manganese dioxide and pure hydrochloric acid in a strong flask with a curved outlet tube from the neck. The stream of chlorine was led to the bottom of another flask, also kept slightly heated, in which lay a saturated solution of potassium bromide. I placed the solution to be brominated in an ordinary Soxhlet fat extraction tube, allowing the bromine to enter by the thin looped tube at the bottom, so that it bubbled up through the contained fluid. By this means the sudden precipitation of the halogen compound is well demonstrated. By variations in the degree of heat applied to the two flasks the quantity of bromide applied, as shown by the rate of bubbling into the Soxhlet tube, could be maintained uniformly. The time taken for precipitation varied from three quarters of a minute to seven minutes, with no obvious cause except individual differences in the stability of the nucleo-proteins and their bromine affinity. A similar but less satisfactory result was obtained by quickly passing a few drops of bromine in liquid form to the bottom of a large Stokes' tube containing the solution, and then agitating the tube.

Examination of solutions which have been subjected to bromination, but not to the degree of precipitation, showed the

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important fact that a slightly larger amount of acetic acid is required to effect precipitation of the nucleo-proteid than in a simple solution through which no current has been passed. Bromine precipitate likewise requires the addition of slightly more alkali for solution than the simple precipitate. This difficulty in precipitation and resolution increases as time elapses, and I have found that a bromine precipitate kept for two months in a stoppered tube is very slowly soluble even in 5 *per cent.* sodium hydroxide. This also applies in a less degree to the non-brominated precipitates.

In addition to the alkaline solution the blood plasma and cerebro-spinal fluids exhibit a similar sudden precipitate on bromination, but, owing possibly to the small quantities available, I was only able to be sure of the presence of phosphorus in two cases of blood plasma out of four, and in none of the cerebrospinal fluids, of which I tried five.

Phosphorus was present in all the bromine precipitates of nucleo-protein from brain. It is probable that the action of the bromine is to precipitate the nuclein, and a varying protein moiety. Whether this is due to the substitution of hydrogen by bromine in the molecule is not known. From the behaviour of the precipitate in the partially brominated solution I have come to the conclusion that the effect of the halogen union is to fixate the large nucleo-proteid molecule, and render it less liable to rapid change. If this be so the presence of bromine in the nucleo-protein of the living cells would act as a restraining influence upon its metabolism.

This view was formed chiefly upon the foregoing observations of increased resistance to change of physical state. The action of the bromide salts upon the albuminous bodies of a sensitised photograph plate in restraining the rapid chemical changes therein on exposure and development is interesting.

Albertoni (73) has observed that a considerably stronger current of electricity is required to excite the cortical motor neurons of a dog which has been dosed with bromide. The iodine content in the iodothyreoglobulin has been shown to be high after potassium iodide administration (74), and Falta (75) states that "iodised albumens are metabolised more slowly than simple albumens."

In addition to the glycogen reaction of the blood which is found in certain serious conditions, an intra-cellular and

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extra-cellular iodin reaction has been shown to be present in physiological conditions (76). By the action of iodine vapour on moist smears a granular staining of the protoplasm of the lymphocytes, and a diffuse staining of the polymorphs have been exhibited. A similar extra-cellular iodin reaction has also been found which Gabritschewski and Zollikofer have shown to be masses of blood plates. This extra-cellular reaction is also found at times in healthy blood, and in states of acidosis such as diabetes, the cause for its variability in healthy blood not being known. I examined a number of epileptic bloods by this means, and was surprised to find the reaction present in six out of the first eight cases which I tried. I substituted bromine for iodine vapour, and was impressed at once by the appearance of a marked reaction in my own blood, distinct extra-cellular granules being observable, and the nuclei, especially those of the polymorph cells, being very well defined. I am convinced that the extra-cellular elements consisted of blood plates, and I believe that the variations in the stainability of the intra-cellular granules is exactly comparable to the changes in the affinity for the basic dyes observed by Gage and Mann which will be described in a later paragraph. If my assumption, that the stainability is dependent upon the nucleo-proteid content of the blood, be correct, its greater definition in the hypo-alkaline or slightly acid states such as diabetes and uræmia is explainable. I obtained well-marked positive results, by a variation of the method in every epileptic case which I examined. A strong aqueous solution of bromine water was prepared, and a drop of this was mixed with an equal sized drop of freshly drawn blood upon a cover slip, and at once mounted in levulose upon a slide. Stained in this way the nuclei of the leucocytes are exceedingly well-defined, and the blood plates can easily be counted in relation to the leucocytes, the red cells being to a large extent hæmolysed. These blood plate enumerations vary, however, so greatly in slides prepared from the same cases at the same time that no statement as to their number would be of the slightest use, and I believe that their variation was not due to the staining method, but to the great rapidity with which the blood plates change in number in shed blood in process of extrusion from, or disruption, of the polymorph cells, and in their speedy disappearance as entities as they interact with prothrombin to form thrombin. The

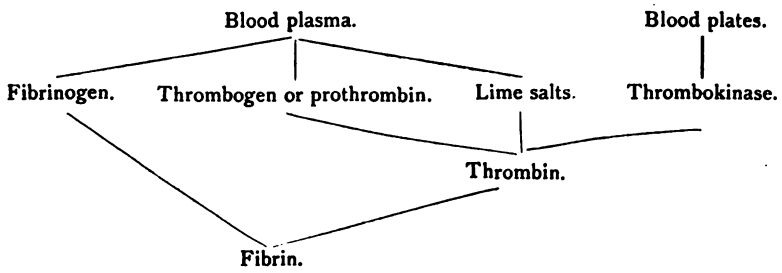
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widely different results which all observers have obtained in blood plate enumerations contrasted to the counts of the real formed elements, the white and red corpuscles, support this view, and any comparative estimation made by any method is liable to be fallacious, unless the fixation of the plates can be effected at precisely the same second from the time at which the blood leaves the blood channels.

In the blood, as in the brain, the nucleo-protein content is high, and is of great importance in the production of agglutination and coagulation. The viscosity and coagulability of the blood can be altered by dietetic and medicinal means by the increase of ingested nucleo-proteid and its components.

The disruption of the polymorph cells increases the purin content of the blood, and so the secretion of uric acid. We have seen that the sudden introduction of nucleo-proteid in excess into the blood of animals is productive of extensive intra-vascular coagulation, epileptiform seizures, and, with sufficient amount, death. We also know from the observations of Turner that the nucleo-proteid coagulative elements are found in excess in the cortical blood vessels of epileptics and, from the observations of Mott, that a biochemical change occurs in the cortical cells rich in nucleo-protein dependent upon the condition of the surrounding lymph.

The theory of fibrin formation in most general acceptation may be illustrated thus: (77)



A large increase in the polymorph leucocytes takes place after the ingestion of protein-rich food (78). The proteins are the chief agents in the production of the so-called digestion leucocytosis, being more effective in this way than the fats. Gage and Mann (79) have also shown a large increase in the nucleo-protein elements of the blood, and an increase in their stainability,

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after the ingestion of protein substances, and of the phosphorus-rich substance sanatogen.

It has been shown (80) that the injection of nucleinic acid constantly causes a hyper-leucocytosis, without increase in the mononuclear cells. The assimilation of nuclein-rich foods causes increase in the output of the purin bases and uric acid in the urine. Purin bases when assimilated also increase the uric acid excretion; this in part is due to a direct alteration in the purin bodies and the blood, and partly to a disintegration of the nucleo-protein of the cells (81). In leucocythemia, in which there is an excessive leucocyte formation and destruction, the purin bases of the blood and urine are markedly increased (82). Albumosuria is common and a diminished alkalinity of the blood is stated to be present (83).

We know that a great destruction of the leucocytes takes place on coagulation, and this is most marked in the polymorphs.

The relation between diminished alkalinity of the blood and increase in the viscosity and coagulability of the blood has also been mentioned. That the blood in epilepsy at all times, and especially immediately prior to a fit, is hypo-alkaline has been demonstrated, and also the relative decrease in the polymorph cells after a convulsion.

Lowit (84) has observed that agents which when injected intra-venously cause a leucocytosis, produce, as an immediate primary result, a leucolysis; among such substances are peptone, nuclein, and uric acid.

These facts, together with the evidence in the urines of nucleo-proteid decomposition in the uric acid, phosphates, and albumosuria, are strong indication that such a change in the leucocytes occurs at the convulsive period, with its attendant coagulative effect. The presence of the nucleo-proteid coagulants in the cerebral blood vessels strengthen this opinion.

A considerable reduction in the alkalinity of the blood in the acid states, such as diabetes, uræmia, and eclampsia, in all of which convulsions occur, has a further effect. In all acid intoxications the calcium content of the blood increases, apparently at the cost of the tissues (85). Very slight alterations in the percentage of calcium causes profound change in the nucleo-proteid substances (86). I consider it highly probable that in the increasing acidity of the blood in status epilepticus the calcium content of the blood increased in this

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way, and so develops the stasis and agglutination which produce the ordinary fit into a coagulation with fibrin formation, which produces in most cases death.

We have seen the effect of the mass action of CO_2, suddenly applied, in increasing the alkalinity of the serum. I believe that this change tends to prevent further leucolysis when the convulsion has once taken place. Along with the increased pulse rate, the rise in blood pressure and the aid of anastomotic channels, the sudden cyanosis thus acts as a remedial agent in a convulsion.

The Exciting Cause of a Convulsion.

The application of the preceding sections upon the metabolic changes of nucleo-protein in brain and blood to the convulsive manifestation will form the conclusion of this thesis.

The acid products of metabolism—in the body chiefly lactic and carbonic acid, and in the nucleo-protein rich cells, such as the cortex, uric acid, and carbonic acid—these products tend to inhibit the further progress of metabolism. Additional factors also arise. The increase of viscosity of the blood in the capillaries causes a slight slowing of the stream, and a diminished supply of oxygen. The diminution of metabolism is further reflected upon the rate of flow, the metabolic activity of the cells, *per se*, being an influence in stimulating capillary circulation in the cortex, by the rapid movement of the protein atoms and molecules in and between the cells, lymph spaces, and fine capillary channels (87).

The result of prolonged mental exertion produces physiological indicants to rest in drowsiness, impaired perception, and dulling of the special senses, along with impaired motor control. If the required rest be not afforded these symptoms develop into headache, irritability, and, in advanced fatigue, a tendency to insomnia by the morbid stimulation of the exhausted cells by the toxic accumulants. If, however, rest be given in the earlier stages of fatigue, sleep ensues. To effect this state of rest, the stimulation of the special senses is diminished by darkness and silence. The adoption of the recumbent position causes congestion of the cerebral vessels. These vessels dilate, and this in the cortical regions causes the entrance of the lymph with its acid contents into the blood stream, and further

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increases viscosity. The slackening of the stream is increased by the lessened force of the heart's action, by a slight fall in the blood pressure, and by the diminution in the effect of the respiratory pump as respiration becomes slow and shallow. The application of warmth also favours agglutinative change.

The result of the interaction of all these factors is a gradual "sleepening," and ultimately sound sleep, when metabolism in the cortical areas is at a standstill. The reflex pontomedullary centres, which control the vital functions, are not similarly affected because of the differences, already mentioned, in the calibre of the capillaries, and the completely different lymph vascular arrangement which exists in all regions outside the cortex.

As the viscosity and sluggishness of the cortical capillary stream increases the sleep deepens, and it has been demonstrated experimentally that viscosity is greatest at the time of deepest sleep.

The acid accumulants are gradually removed from the blood by the kidneys and skin, and the capacity for action of all the cells of the body and brain is slowly but completely restored. As the alkalinity increases, the proclivity to rapid metabolism reappears, and slighter and slighter stimuli will provoke excitation of the cortical cells, and a return to consciousness.

In relation to these phenomena, which are gradual and self-regulative in their action, there are numerous deviations in the healthy subject which are relevant and important.

After excessive exertion, especially mental, a familiar occurrence is the sudden start which rouses an incipient sleeper. "It is an insubordinate action of the motor centres occurring during the gradual withdrawal of the higher control" (88). It is due in my opinion to a sudden degree of stasis produced by the entrance of the acid katabolic substances to the blood stream from the large lymph spaces in the motor areas, so suddenly effected that a sudden failure in the oxygen supply is produced instead of a slow diminution.

Sudden night terrors, and the phenomena of somnambulism are due, I believe, in a large measure to an absence of harmony in the progression of the various factors which produce and maintain unconsciousness.

If the cardiac action be irregular, agglutination may occur on a sudden fall in the pulse rate when the highly viscous blood

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is slowly passing through the capillaries, and a sudden increase in the carbon dioxide in the lymph takes place, a morbid toxic stimulation of the cells occurs, and the phenomenon of the Stokes-Adams seizure is evinced.

If, on the other hand, an ordinary syncopal attack occurs by day the blood pressure falls more slowly, and, the blood not being in an especially agglutinative state, unconsciousness is produced with less rapidity.

If the defective factor be the blood and lymph contents, a state of narcolepsy may be similarly produced at any hour of the day, but especially after meals, by a comparatively slow degree of morbid cortical stasis.

These conditions form the connecting link between the one extreme of healthy physiological conditions of cortical activity and inactivation, of waking and sleeping, and the other extreme of the epileptic state in which the blood and lymph anomalies take effect so quickly that the morbid excitant effects of stasis are produced instead of the slow and gradual unconsciousness.

In the epileptic, metabolism is at all times carried on in the minimal degree of alkalinity of the blood and lymph, and the equilibrium of the cerebral circulation, delicate in the healthy, is reduced to an extreme degree of instability in epilepsy. Any excitant to further increase in viscosity, stasis, and agglutination, may provoke a convulsion, and thus we find the attacks occur at the times when there is a natural slight tendency to stasis, at the inception of sleep, and in the hours of deep sleep, and when the coagulative elements of the blood are high after the ingestion of nucleo-protein and purin.

The decrease in the poly-nuclear cells, which are coagulative elements, and the appearance in the urine of the decomposition products of coagulative bodies serve to indicate that agglutination must have occurred. The discovery of evidence of such agglutination in excess in the epileptic brain supports this statement. The effect of the administration of the alkalies in raising the blood state from the danger level of marked hypo-alkalinity, of the bromides in fixating the cortical acid producing substances and the coagulative elements of the blood, and of digitalis in raising the general level of blood pressure, lend support from the therapeutic standpoint to this view.

I believe that the epileptic phenomena are due to a morbid development of one factor in the natural physiological *régime*,

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the reduction of alkalinity dependent on metabolism, and the effect of the comparative acidulation of the serum upon the coagulative elements in the blood, that this acidulation of the lymph and blood is produced by too rapid metabolism of the nucleo-proteid of the cortical cells and other nucleo-protein containing tissue, which also, in the circulating media, show a proclivity to an abnormally rapid agglutination, and that the primary cause is an inherent defect in the nucleo-proteid tissue elements which may be hereditary.

General Summary.

The manifestations of epilepsy, the convulsive seizure, and the minor attack are due to a sudden anæmia of the cortex causing a discharge of the cortical nerve cells.

This anæmia is produced by a sudden stasis and agglutination of the nucleo-proteid coagulative elements of the blood in the cortical capillaries.

An unusual proclivity to agglutination, and a hypo-alkaline state of the blood, exists in epilepsy, which renders such a stasis possible at any moment.

Such a sudden agglutination may be produced when the nucleo-proteid elements of the blood are increased by ingestion of nucleo-protein and purin bodies, and at the inception of sleep and advancing stages of its profundity.

The post-paroxysmal changes in the blood and urine indicate that a rapid disintegration in the nucleo-proteid elements has occurred.

The *post-mortem* findings indicate the excessive production in the brain of such nucleo-proteid agglutinations in the cortical capillaries, and an excessive biochemical change in the cortical cells which are rich in nucleo-proteid.

The administration of alkalies reduces the coagulative tendency, but, by facilitating metabolism, cannot reduce the number of the convulsive attacks other than temporarily. The bromides have a particular affinity for the nucleo-proteins, and act by inhibiting their rapid metabolism ; this diminishes the acidulation by uric acid of the contents of the cortical perivascular lymphatics and capillaries, and also renders the polymorphonuclear cells, and the other nucleo-proteid coagulative

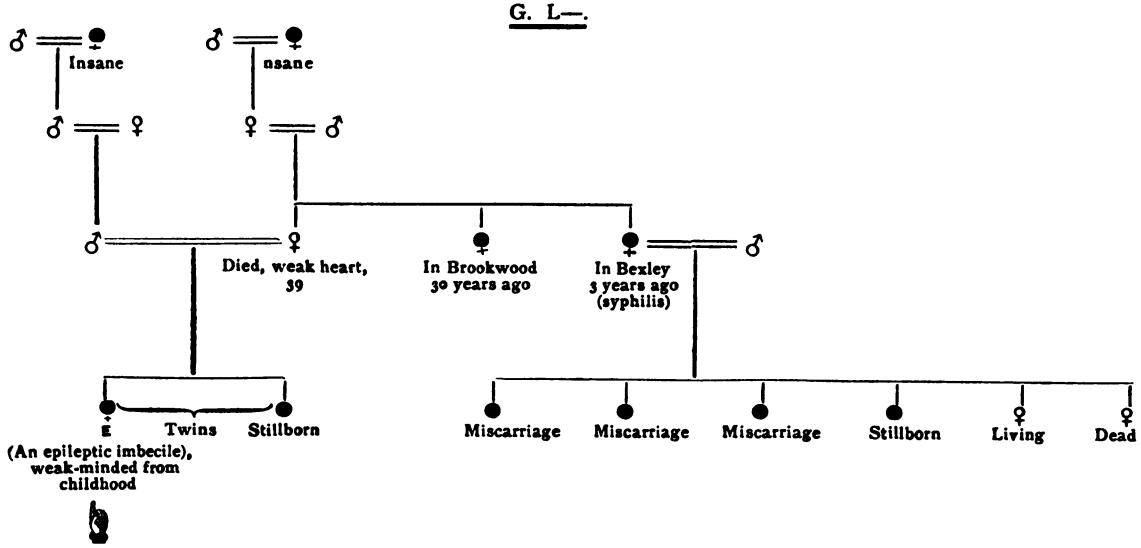
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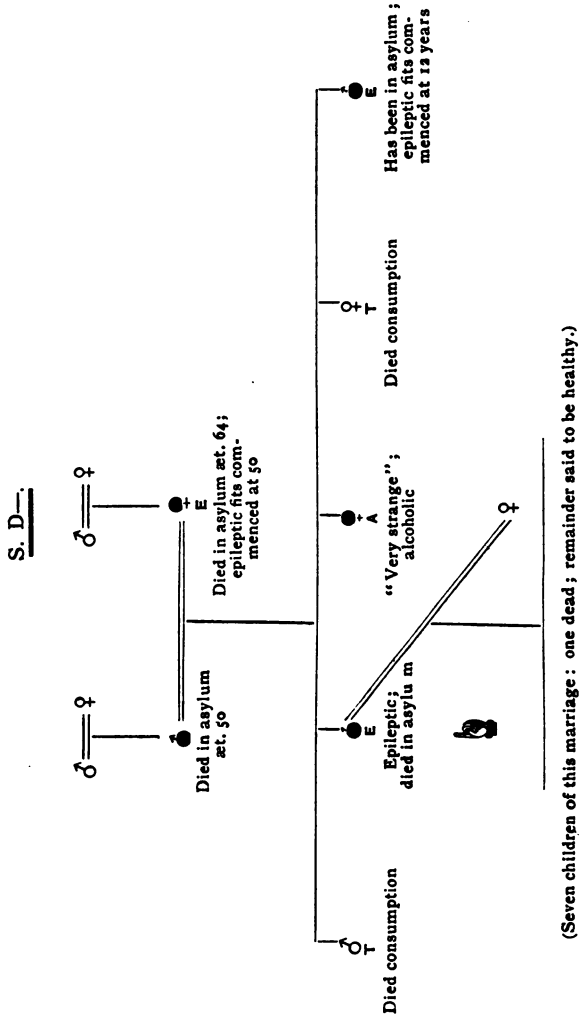
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APPENDIX A.—*Heredity Tables of Three Epileptic Patients with Epileptic and Insane Heredity, and of Three Non-Epileptic Cases with Epileptic Heredity.*

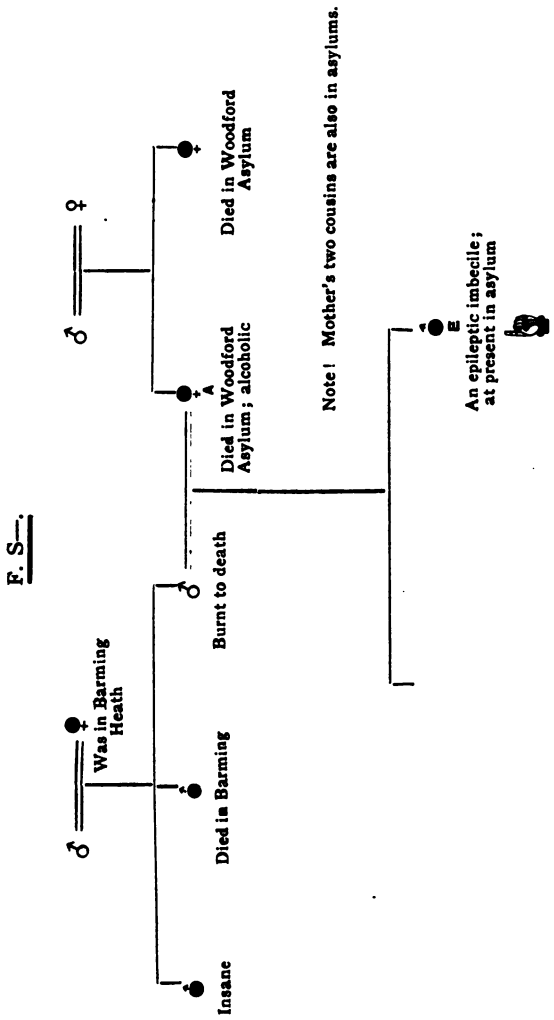
KEY TO CHARTS.

♂ = male. ♀ = female. ● = miscarriage or still-birth. ♂ = Male insane or imbecile. ♀ = female insane or imbecile. The hand indicates position of patient in sequence. The letters E, A, T underneath signs indicate epilepsy, alcoholism, and consumption respectively.



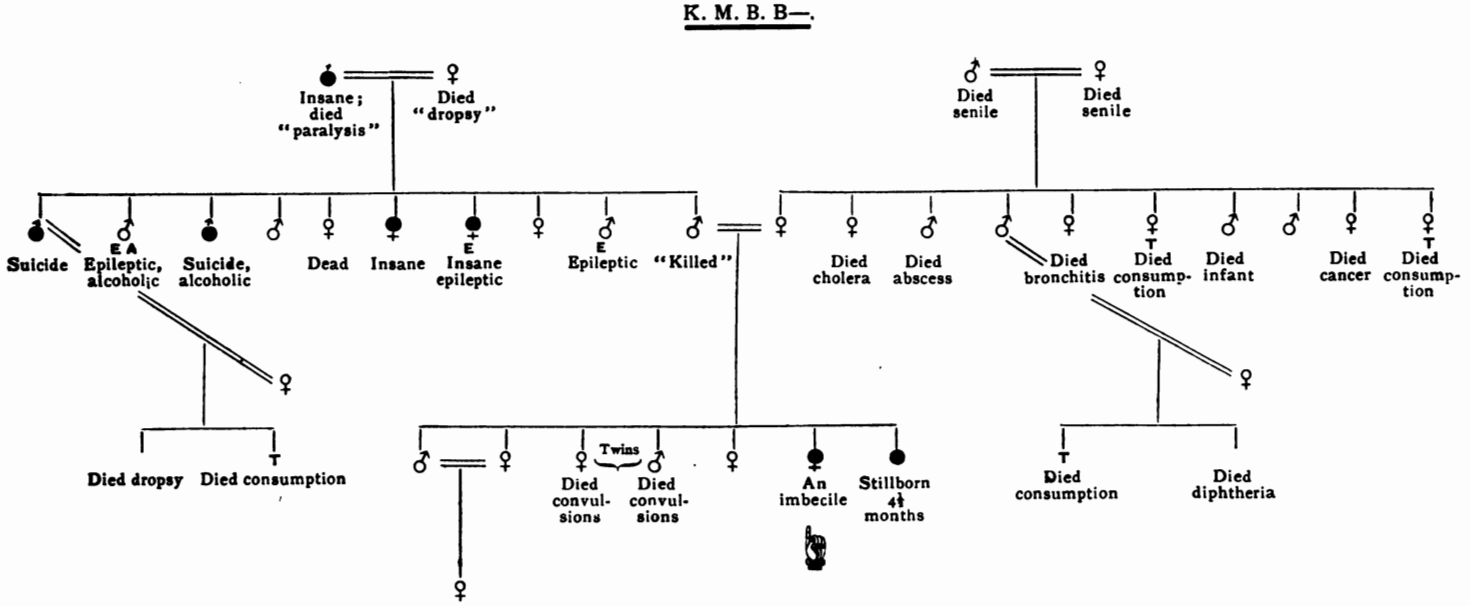


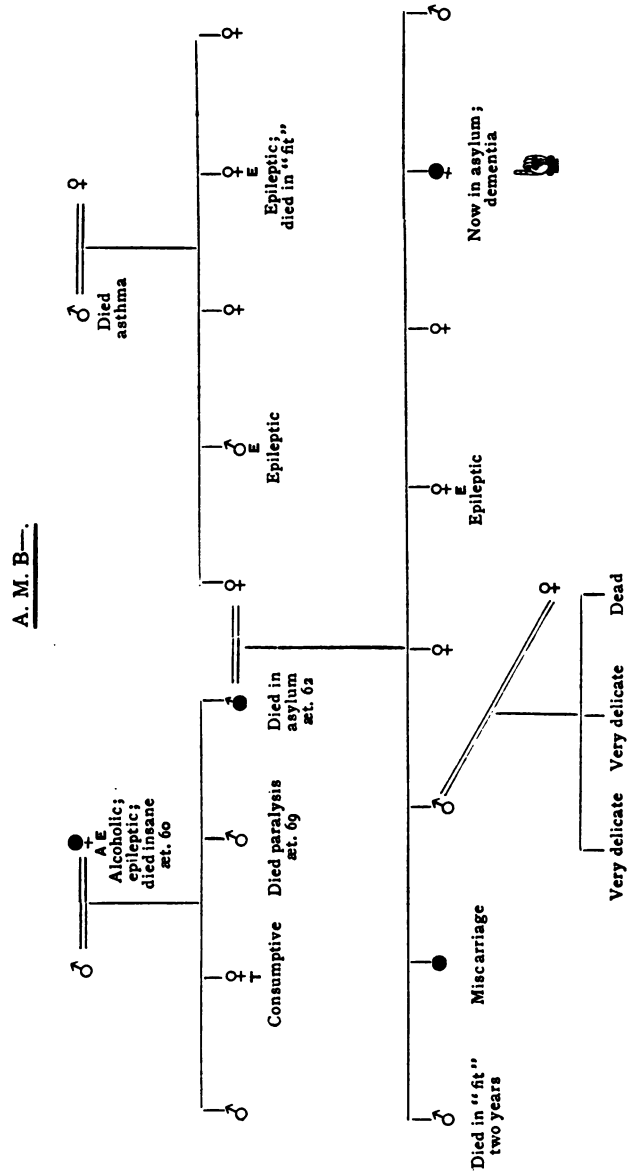
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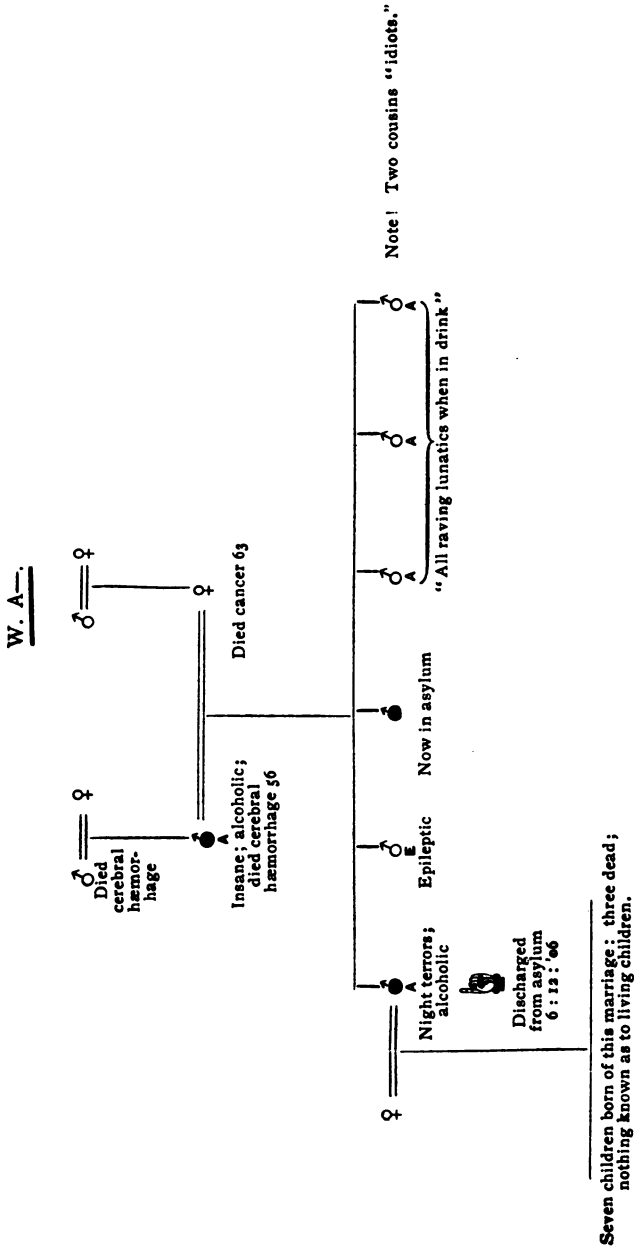
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W. A—.
Died cerebral hæmor-hage
Insane; alcoholic; died cerebral hæmorrhage 56
Died cancer 63
Night terrors; alcoholic
Epileptic
Now in asylum
"All raving lunatics when in drink"
Note! Two cousins "idiots."
Discharged from asylum 6 : 12 : '86
Seven children born of this marriage; three dead; nothing known as to living children.

elements of the blood, less liable to sudden change. The oxalates are of definite value in the treatment of epilepsy.

The inherent defect is in the chemical instability of the nucleo-proteid elements of the brain and blood, which may be hereditary, or due to the absence of a regulating hormone, at present unkown.

For the privilege of using the clinical material embodied in this thesis I am deeply indebted to Dr. Stansfield, Medical Superintendent, and to the Bexley Sub-Committee of the L.C.C. Asylums Committee.

Appendix B.

From observation of the action of the blood of epileptics I am convinced that the agglutinative action is one of unusual rapidity.

Working with all possible speed, and drawing the drops as soon as intermixed into the long tube, I managed to obtain a fairly large number of samples. But using the method recommended by Wright, which is quite simple in non-epileptic blood, of making the series of intermixtures on the slide, and then proceeding to draw them one by one into the long tube for observation, I never improved upon the percentage of agglutinations which impressed me upon the first trial of epileptic blood in which only five out of a total of thirty-two intermixtures could be drawn into the tube.

As I soon became aware that the results from the point of view of the calcium content would be worthless, I used only three of Wright's dilutions ($\frac{N}{80}$, $\frac{N}{180}$, $\frac{N}{320}$ ammonium oxalate in physiological saline) and supplemented them by two strong solutions of sodium chloride (15 *per cent.* and 30 *per cent.*), two similar solutions of calcium chloride and one drop of unmixed blood.

I regret now that I did not attempt to estimate the calcium by Blair Bell's calcimeter after trying Wright's method, but had I done so at first (in Blair Bell's method the blood is drawn straight from the drop at the site of puncture, with no exposure on a slide) I might not have observed the rapid agglutination to which great importance is to be attached. To determine the presence of clot, unless its distinct formation could be seen in the capillary tube, I expressed them into water. Before estimating the results the tubes were kept for twelve hours in a Hearson incubator at 37° C.

Eight Examples of Ammonium Oxalate Dilution of Blood.

Non-Epileptic.

W. D— (M.).—Calcium content $\frac{N}{80}$ no clot / $\frac{N}{100}$ clot = 0·58 parts of Ca O in 1,000.

W. M— (M.).— „ „ $\frac{N}{120}$ no clot / $\frac{N}{150}$ clot = 0·41 „ „ „

J. J. M. S—(M.).— „ „ $\frac{N}{200}$ no clot / $\frac{N}{240}$ clot = 0·26 „ „ „

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S. A. B— (F.).—Calcium content $\frac{N}{100}$ no clot / $\frac{N}{120}$ clot = 0·5 parts of Ca O in 1,000.

In this case dilution $\frac{N}{280}$ agglutinated on slide, the only such instance among non-epileptics.

E. E. B— (M.).—Calcium content $\frac{N}{200}$ no clot / $\frac{N}{240}$ clot = 0·25 parts of Ca O in 1,000.

A. W. P— (M.).— „ „ $\frac{N}{180}$ no clot / $\frac{N}{200}$ clot = 0·29 „ „ „

W. E.— (M.)— „ „ $\frac{N}{200}$ no clot / $\frac{N}{240}$ clot = 0·25 „ „ „

Epileptic.

J. R. H— (M.).—All mixtures except $\frac{N}{150}$ agglutinated on slide, and could not be drawn into tube.

F. D. H— (M.).—The last two intermixtures only could be drawn in, and these did not clot.

H. O. M— (M.).—Several stabs required before blood flowed sufficiently. All agglutinated on slide before intermixture.

J. McC— (M.).—Two only obtained $\left(\frac{N}{240} \text{ and } \frac{N}{280}\right)$; neither clotted in tube. On expression into water the small amorphous masses dispersed at once.

A. W— (M.).—Three weaker solutions only obtained; no clot in tube.

R. B— (M.).—All agglutinated before intermixture.

R. W— (F.).—Four dilutions obtained; no clotting in tube.

E. H— (F.).—Three obtained; slight clot (which sank to bottom in water in white porcelain dish and then broke up) formed in $\frac{N}{240}$ dilution.

M. H— (F.).—All except $\frac{N}{100}$ and $\frac{N}{280}$ agglutinated before intermixture, and none could be drawn into tube for observation.

Three Samples of Ammonium Oxalate Dilution ($\frac{N}{80}$, $\frac{N}{180}$, $\frac{N}{320}$), *Two of Sodium Chloride, Two of Calcium Chloride, and One Unmixed Drop of Blood.*

Epileptic.

A. C. G— (M.). All agglutinated on slide. Only a few minute drops of the fluid mixed with air bubbles could be obtained from the base of the drop. If the point of the tube was placed in the middle of the drop and suction applied, the agglutinated mass formed a plug and did not enter the tube.

D. A. W— (M.). All ammonium oxalate dilutions; the weaker calcium

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chloride, and the unmixed drop were obtained. No coagulation occurred in ammonium oxalate; in calcium dilution a true retractile clot formed; the unmixed drop agglutinated, and lay along the wall of tube.

From the remainder of the cases (five male and six female) I likewise obtained no information regarding the calcium content, as in no case did coagulation occur in the ammonium oxalate dilutions. In all the instances (4) in which they were drawn into the tube a true retractile clot formed in the calcium chloride solutions.

In seven similar instances (out of a total of eight obtained) retractile clots formed in one of the sodium chloride solutions.

In only one case (G. F. G— (M.)) did a true clot form in an unmixed drop out of eight obtained.

From these results I make the following deductions:

That an unusual proclivity to agglutination on exposure, and on contact with a foreign body, exists in epileptic blood.

That epileptic blood, except when mixed with fairly strong solutions of the chlorides of calcium and sodium, rarely forms a true strong retractile clot in a capillary tube.

Appendix C.

Differential Leucocyte Count.

Out of eleven differential counts in patients who were having frequent fits in only three instances was I successful in making a count at an interval not longer than one hour before a convulsion, beyond which limit I did not consider the count could reasonably be termed pre-paroxysmal. In these three cases I managed to draw blood for the post-paroxysmal count within ten minutes after the cessation of clonic spasm. The results of these differential counts show a relative decrease of polymorphonuclear cells of a varying degree, and in all cases an increase in the total leucocyte count.

	Pre-paroxysmal.				Post-paroxysmal.			
	Polynuclears.	Large lymphocytes.	Small lymphocytes.	Eosinophiles.	Polynuclears.	Large lymphocytes.	Small lymphocytes.	Eosinophiles.
	per cent.	*per cent.*	*per cent.*	*per cent.*	*per cent.*	*per cent.*	*per cent.*	*per cent.*
G. C— (M.)	78	7	13	2	61	12	23	4
	White blood-corpuscles 9800				White blood-corpuscles 12200			
J. Mc. C— (M.)	74	5	20	1	71	11	15	3
	White blood-corpuscles 11200				White blood-corpuscles 11800			
A. W— (M.)	69	8	21	2	61	6	28	5
	White blood-corpuscles 11400				White blood-corpuscles 12400			

The other differential counts showed no marked abnormalities except an eosinophilia of *7 per cent.* in one case.

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Appendix D.

Estimation of Urinary Changes.

In the examination of the pre- and post-paroxysmal urines on eighteen occasions of *grand mal*, and on five occasions of *petit mal*, the uric acid estimations were made by heating five drops of urine with one drop of pure nitric acid in a white porcelain dish. When evaporation was almost complete a drop of liquor ammonii fortis was placed at the edge of the residue, and the absence of change, or the intensity of the purplish colouration, gave a fair indication of the quantity of uric acid present. In two female post-paroxysmal urines distinct uric acid crystals were visible (89).

The albumose test was carried out by heating 5 c.c. of urine, filtered if necessary, with ten drops of a saturated solution of picric acid; if the resultant solution was perfectly clear it was allowed to stand for one hour and the appearance of a distinct cloudiness was taken as a positive reaction. In the cases which I examined by the half and complete saturation with ammonium sulphate, I found both primary and secondary albumoses were present. In some cases crystallisation of uric acid occurred in these positive albumose solutions (90).

The constant increase in the quantity of mucin passed was very striking. We should expect that changes in the blood and lymph which affect the nucleo-protein should also affect the mucin elements whose solubilities are exactly similar in the body fluids.

In eighteen consecutive examinations of the last urine voided before the convulsive attack, and the first voided after, the uric acid content was in each case increased; the albumose was increased in fourteen cases, the mucin was increased in seventeen cases.

In five cases of *petit mal* the uric acid was increased in three cases, the albumose was increased in three cases, the mucin was increased in all.

In no case was the quantum of any of the three substances diminished after the convulsion, but the degree of change was less marked in *petit mal* than in *grand mal*.

Appendix E.

Phosphate Excretion in Two Cases.

The total excretion in both cases was comparatively low. The dietary of an asylum, and the comparative lack of exercise, are the probable causes of this condition. The excretion is greater after the convulsive attack.

The striking change in the time incidence of the convulsions in H. O. M— followed the substitution, on April 1st, of a pint of breakfast coffee for a pint of cocoa.

Sanatogen produced a rapid and pronounced deleterious effect on this patient, increasing the number and severity of his attacks; during the time of its exhibition he was in a state of confusion and unable to work.

The quantitative phosphate estimations were made by the uranium nitrate titration method, with tincture of cochineal as indicator (90).

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Appendix F.

Summary of Treatment.

In addition to the bromides of ammonium, sodium, and potassium, I have observed the effects upon epileptic patients of the following substances: Ammonium oxalate and oxalic acid, calcium chloride, calcium lactate, calcium glycerophosphate, sodium carbonate and bicarbonate, lecithin, liquor thyroidei, sanatogen, phytin liquidum, parathyroid extract (I obtained a small quantity of this substance from Messrs. Allen and Hanbury; prescribed in cachet in 2 gr. doses twice a day, it produced no effect in two cases, and its cost precluded more thorough investigation).

In all the cases which were treated I omitted all medicine except the ordinary institution aperients for at least three weeks in patients who were having frequent fits, and for periods of two or three months in patients who had few fits. No patients whose fits occurred in cycles were chosen for therapeutic investigation, as fallacious conclusions of success or failure might have resulted from their irregular manifestations.

From the administration of oxalic acid and ammonium oxalate I obtained very good results in thirteen out of sixteen cases. Their most marked effect lay in the shortening of the post-paroxysmal states of stupor and headache, and in the improvement in the patient's mental state in the interparoxysmal period. One example of the change in manner of recovery I have already described (p. 27), and in varying degree this effect was observable in all the cases.

In three cases, along with a reduction in the total number of paroxysms, the minor attacks almost entirely disappeared.

Of the three cases which I consider unsuccessful, two were patients who were having infrequent fits, which were not inhibited by oxalic acid, as could be done by bromide. The third case was interesting. On large doses of bromide (ammon. brom., pot. brom., stront. brom. ā.ā. gr. x, t.i.d.) the patient had an average, over five months, of nine fits per week. When I omitted the bromides he immediately commenced to have a large number of nocturnal fits, from three to six per night, and after five days in this condition I commenced the small doses of oxalic acid. This produced no effect in reducing the number of his attacks in seven days, and I was forced to restore the bromides to him. It is now seven weeks since the bromides were restored, and his average number of fits is still high compared with his original state on bromides. The attacks in this patient are almost entirely nocturnal in his normal routine, but when kept in bed during the day for mental or physical reasons, his postural incidence is shown by frequent attacks. His nocturnal attacks were not, however, diminished by sleeping in a semi-recumbent position.

The beneficial effects upon two of the thirteen cases became less marked after the expiry of five weeks in one instance and seven in the other. By the administration of 1 gr. of oxalic acid in the morning and 10 gr. of bromide in the evening, in these two cases the total number of fits is still much below that of the period in which no medicine was given. I prescribed these substances as follows:

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℞ Oxalic acid, gr. ½ (or ammon oxalat., gr. 1)
Aq. ad., ½ oz.
Four times a day one hour before meals.

In no case have I observed the slightest ill effect with these doses. My original use of oxalic acid was the result of a conviction that the epileptic manifestations were produced by an agglutinative or a coagulative process. From citric acid I obtained no results, and, finding that oxalic acid had been used therapeutically in scurvy, I determined to try it, and I consider the results very gratifying. Of the two substances I prefer oxalic acid to ammonium oxalate. The immediate recrudescence of the post paroxysmal symptoms in several cases, when these substances were omitted and bromides prescribed, has convinced me of their usefulness.

It is highly probable that the oxalic acid acts by inactivation of the calcium of the blood as a coagulative factor. Its presence does not inhibit agglutination outside the body in epileptics, as has been shown in Appendix C. I consider it probable that the oxalates may neutralise the excess of calcium which is drawn from the tissues in the markedly hypoalkaline states, and so may diminish the tendency to disruption of the polymorph cells which in excess of the ordinary calcium salts in the blood will effect. In this way the earliest factor favouring agglutination, the excess of blood plates, may be counteracted, although the addition of the oxalates to the shed blood in which the disruption has already occurred cannot stay agglutination. Cramer and Pringle (92) have shown that the effect of the oxalates is to keep the blood-plates intact and so prevent coagulation. I believe it is probable that the rapid recovery after convulsions, shown by patients on the oxalates, may be due to the limitation of the blood-plates to their mechanical effects in contradistinction to their chemical potentialities.

The exhibition of the calcium salts produced a slight increase in the number of the fits, and in some cases a striking change in their character in the way of a marked lengthening of the pre-convulsive stage of twitching or rigidity. It is probable that the comparatively slight effects produced by calcium are due to the difficulty of raising the calcium content of the blood by therapeutic means which Addis has demonstrated. I prescribed calcium as follows:

℞ Calc. chlor., gr. xx (or calc. lact., gr. xx).
Aq. ad., 1 oz., *t.i.d.*

℞ Calc. glycerophos., gr. xx.
Aq. aurant. ad. 1 oz., *b.i.d.*

From the alkalies, sod. carb. or bicarb. (gr. xxv) *t.i.d.*, I obtained very good effects, the number of fits being, in some cases considerably reduced and the mental state improved. Glycerine of lecithin (ʒij, *b.i.d.*) had no marked effect nor had liquor thyroidei, ♏x, *t.i.d.*

Sanatogen (ʒj, *b.i.d.*) and, to a less degree, phytin liquidum (a vegetable preparation containing calcium and magnesium phosphate with diphosphoric acid) (ʒ ½, *t.i.d.*) produced a definite increase in the number and severity of the convulsions.

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Appendix G.

Sex and age.	Epileptic or non-epileptic.	Heart.	Blood vessels.	Blood pressure.	Pulse mobility.					*Tache cérébrale.*	Capillary pulsation.
					Before rising.	Average.	After rising.	Average.	Difference.		
M., 32	E.	o	+ slight	195	51, 50, 55	52	59, 65, 66	63	11	—	—
M., 66	,,	o	+ slight	135	61, 55, 56	57	68, 70, 68	69	12	—	—
M., 18	,,	o	—	117	63, 71, 70	68	88, 93, 87	89	21	—	—
M., 26	,,	o	—	142	74, 66, 60	67	78, 89, 77	81	14	—	—
M., 23	,,	o	—	135	51, 55, 50	52	52, 59, 53	55	3	—	—
M., 36	,,	o	—	122	61, 66, 70	66	86, 80, 90	86	20	—	—
M., 39	,,	o	—	140	61, 64, 67	64	87, 90, 99	92	28	—	—
M., 51	,,	+	+	138	72, 72, 74	73	97, 100, 105	101	28	+	—
M., 65	,,	+	+	220	87, 75, 80	81	106, 82, 88	92	11	—	—
M., 22	,,	+ mitral incompetence	—	135	93, 87, 90	90	127, 117, 120	122	32	+	—
M., 79	,,	+	+	148	85, 87, 86	86	95, 98, 101	98	12	—	—
M., 23	,,	o	—	130	52, 52, 50	51	83, 94, 99	92	41	—	—
M., 36	,,	o	+ slight	109	66, 60, 61	62	82, 76, 74	77	15	+	—
M., 49	,,	o	+ slight	140	77, 71, 74	74	99, 96, 83	93	19	—	—
M., 43	,,	o	—	145	71, 72, 81	75	90, 88, 102	93	18	—	—
M., 72	,,	+	+	145	68, 75, 61	68	84, 84, 80	83	15	+	—
M., 34	,,	o	—	143	71, 74, 59	68	90, 87, 77	85	17	—	—
M., 46	,,	o	+	152	68, 80, 72	73	71, 84, 79	78	5	—	—

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Sex and age.	Epileptic or non-epileptic.	Heart.	Blood vessels.	Blood pressure.	Pulse mobility.					*Tache cérébrale.*	Capillary pulsation.
					Before rising.	Average.	After rising.	Average.	Difference.		
M., 48	E.	+	—	149	71 79 74	75	101 111 96	104	29	+	—
F., 20	,,	0	—	140	87 66 77	77	91 80 75	82	5	+ slight	—
F., 23	,,	0	—	145	59 74 63	65	78 80 75	78	13	+	—
F., 37	,,	0	—	160	71 79 74	75	87 91 88	89	14	—	—
F., 39	,,	0	—	145	59 53 60	57	91 92 99	94	37	—	—
F., 26	,,	0	—	125	86 79 81	82	84 86 90	90	8	—	—
F., 54	,,	+ irregular	—	155	72 76 74	74	89 96 91	92	18	—	—
F., 20	,,	0	—	135	74 80 80	78	89 96 99	95	17	—	—
F., 32	,,	0	Slight	130	64 69 63	65	80 99 91	90	25	Slight	—
F., 19	Non-e.	0	—	110	75 65 72	71	87 82 79	83	12	—	—
F., 36	,,	0	Slight	154	78 76 72	75	81 85 82	83	8	—	—
F., 21	,,	0	—	140	55 81 80	72	68 86 81	78	6	—	—
F., 22	,,	0	—	140	73 74 71	73	77 83 77	79	6	Slight	—
F., 49	,,	0	Slight	155	89 59 60	69	98 80 90	89	20	—	—
F., 49	,,	0	—	165	82 84 80	82	107 101 102	103	21	+ +	—
M., 45	,,	0	—	118	69 73 70	71	86 86 82	85	14	—	Slight
M., 46	,,	0	—	212	85 76 77	79	97 93 85	92	13	—	—
M., 40	,,	0	—	120	79 72 69	73	96 84 88	89	16	—	—

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In these charts a general impression is sought of the relative stability of the vaso-motor system in epileptic and non-epileptic subjects.

The charts show—

Heart. A + sign indicates the presence of slight cardiac symptoms of shortness of breath on exertion, palpitation, cardio-vascular œdema of the feet, or irregularity in the rhythm of the pulse. No severe cardiac cases with epilepsy are at present in this institution.

Blood vessels. A + sign signifies palpable thickening of the arterial walls.

Blood-pressure. The maximum systolic pressure taken between 3 and 5 p.m.

Pulse mobility. Three observations on the pulse rate of patients were taken before and after rising on consecutive mornings by the trained staff at my request. I have taken the average of these results in each case to estimate the pulse mobility.

Tache cérébrale. As the criterion of the presence of *tache cérébrale* I took distinct visibility at a distance of six feet.

Capillary pulsation. In all the cases I examined the mucous membrane of the inner side of the lower lip by pressing lightly with a glass slide; + indicates a visible pulsation.

I also made inquiries in all these cases regarding sleep, and any pronounced tendency to dream. Even if the statements of the patients were reliable, the results were not of great importance, but from the statements of the staff the soundness of the sleep appears to be slightly greater among epileptics than among non-epileptics. From these results I conclude: That a slightly greater degree of vaso-motor instability exists among epileptics than among non-epileptics; that in a few isolated cases this instability may be an accessory cause of a convulsion; that the degree of instability is much less than may be seen in many non-convulsive conditions, *e. g.*, exophthalmic goitre and some central nervous lesions; that, with the exception of the grave circulatory disorder in the Stokes-Adams syndrome, vaso-motor instability is inadequate and unproven as a cause of epileptic manifestations.

Appendix H.

Quantitative Estimation of Nucleo-Protein, Ether Soluble Substances, and Brominated Nucleo-Protein.

In making these estimations I early perceived that, with the means at my disposal, the attainment of a high degree of accuracy in the results was not possible, and I have intentionally refrained from basing any deductions affecting the general trend of my thesis upon them. In the specimens of brain which I took for maceration the relative proportion of white and grey matter cannot have been constant, and the method of preparation of nucleo-protein generally employed does not altogether exclude the contamination of other soluble proteins. The only points in these investigations of which I have felt entitled to make use are the solubility and insolubility of the nucleo-protein upon a very slight divergence from neutrality of the solvent, and the effect of bromine in

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producing a precipitate which contained phosphorus from a nucleo-proteid solution.

For the tabulated results, therefore, although obtained by careful measurement and uniform methods, nothing more is claimed than a comparative value.

The results quoted represent, first, the quantity of precipitated nucleo-protein obtained from 70 c.c. of a 100 c.c. mixture of sodium carbonate solution with 16 grm. of brain substance (forty-six cases).

Second, the quantity of the bromination precipitate in duplicate solutions to those of No. 1 (twenty-six cases).

Third, the quantity of ether soluble substances (chiefly lecithin) in the same amount of brain substance (forty-six cases).

The acetic acid and bromine precipitates are estimated by their bulk in c.c. upon centrifugalisation after sedimentation for twenty-four hours in a long graduated tube. The lecithin figures represent weight in grammes for 16 grm. of brain substance. An attempt to precipitate the lecithin from the ethereal solution for estimation by adding acetone was useless, owing to the firm adherence of the particles to the sides of the long tubes.

In proving the presence of phosphorus, which I did in thirty-seven nucleo-proteid precipitates by acetic acid, all the bromine precipitates, and thirty-two lecithins, I also estimated its amount by centrifugalising the white precipitate of ammonio-magnesium phosphate. The amounts were too small to dry and weigh with any accuracy, but by the centrifuge I found that the quantity bore a fairly constant ratio to the amount of nucleo-protein and lecithin.

Brain Substance.

Remove a slice weighing about 60 grm. from the right cerebral vertex, having thoroughly stripped the membranes. Reduce it to pulp within thirty-six hours after death by pounding and pressing through a glass filter funnel with a glass plunger.

Preparation of Nucleo-Protein.

Weigh out 16 grm. of pulp and place it in a glass cup. Add 100 c.c. of aqueous sod. carb. solution (1·5 *per cent.*). Stir thoroughly with glass rod, and allow mixture to stand for twenty-four hours. Filter first through coarse and then fine filter-paper, and precipitate by adding about 6 c.c. acetic acid (1 *per cent.*). Allow to stand for twenty-four hours, and redissolve in ·5 *per cent.* sodium hydroxide, from which precipitate again by acetic acid. The amount of solution which would pass through the filter-papers varied in different cases owing to differences in viscosity, and I was compelled to adopt the standard of 70 c.c. as the quantity from which I proceeded to take a precipitate.

Estimation of Phosphorus in Nucleo-Protein.

Remove water from above precipitate, and partially dry remainder in crucible without charring. To this add and intermix about ten times its

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Form of insanity.	Sex.	Nucleo-protein precipitated by acetic acid.	Nucleo-protein precipitated by bromine.	Lecithins.
		C.cm.	C.cm.	Grammes.
Epilepsy	Male	2·2	—	·9
,,	,,	4·2	4·3	1·32
,,	Female	4·3	4·8	1·1
* ,,	,,	3·8	3·6	·995
,,	,,	3·4	3·9	·74
General paralysis	Male	6·9	—	1·15
,, ,,	,,	2·8	3·1	·82
,, ,,	,,	2·9	2·7	1·08
,, ,,	,,	1·4	1·5	·45
,, ,,	,,	3·4	3·2	·62
,, ,,	,,	4·1	4	·65
,, ,,	,,	3·2	3·4	·61
,, ,,	Female	4·1	—	1·1
,, ,,	,,	6·1	—	1·14
,, ,,	,,	3·8	3·9	·95
Organic brain disease	Male	5	5·1	·7
,, ,, ,,	,,	3·8	4·2	·92
,, ,, ,,	Female	5·2	—	1·02
,, ,, ,,	,,	4·1	4·1	·44
,, ,, ,,	,,	4·5	4·7	·41
Dementia (with marked wasting of brain)	Male	5·9	—	1·15
Ditto.	,,	3·1	—	·92
,,	,,	·9	—	·86
,,	Female	3·2	3·7	·75
,,	,,	1·8	1·9	·97
,,	Male	2·4	2·6	·61
Imbecility	Female	(opalescence but no precipitate)		·78
,,	,,	1·9	2·2	·92
Melancholia (no gross lesion or marked wasting)	,,	1·1	—	·8
Ditto.	,,	1·8	—	·5
,,	,,	5·1	—	1·1
,,	,,	6·1	6·6	1·01
,,	,,	2·4	2·4	·65
,,	,,	4·3	4·6	·73
,,	Male	3·3	—	·92
,,	,,	5·2	—	·72
,,	,,	2	1·9	1·2
Delusional insanity	,,	4·7	—	1·1
,, ,,	,,	5·1	—	·56
,, ,,	Female	4·9	—	1·2
,, ,,	,,	5·1	—	·75
,, ,,	,,	4·2	—	·85
,, ,,	,,	2·2	2·7	·78
,, ,,	,,	4·5	4·4	·8
Chronic mania	,,	3·1	—	·48
† ,, ,,	Male	3·4	4·1	·32

* This specimen of brain was kindly provided by Dr. Spark, Medical Superintendent, L.C.C. Asylum, Banstead.

† The brain of infant which died three weeks after birth, the mother was pregnant when certified.

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bulk of potassium nitrate and sodium carbonate mixture (two parts of potassium nitrate to one of sodium carbonate throroughly mixed), and incinerate. The mass turns black, and if heated too rapidly crackles and sparks. When a hard, white cake forms at the bottom of the crucible, and no black particles remain, add the minimal quantity of water which will dissolve the substance (slight additional heat may be required).

Drive off CO_2 with a small quantity of pure HCl, using pipette, and neutralise by liq. ammon. fort. Filter solution and add about half its bulk of magnesia mixture in the long tube. Shake for two minutes, and allow to stand for twenty-four hours. Remove most fluid above precipitate, agitate and pour fluid with precipitate into centrifuge tube.

Lecithin.

Place similar quantity of pulp in glass cup, and add 64 c.c. of methylated ether. Allow to stand for forty-eight hours, stirring several times, and filter into glass bottle. Allow bottle to remain uncorked (a filmy deposit will appear) until contents can be poured into crucible. Allow further evaporation to proceed until semi-solid (about twenty-four hours) and complete process on water-bath.

Phosphorus estimation from lecithin is similar to that from nucleo-protein, the incineration mixture and viscous lecithin being thoroughly mixed.

The process of bromination I have already described, and the method of determining the phosphorus content is the same as in nucleo-protein precipitate by acetic acid. 35 c.c. of the sod. carb. solution were taken, and the acetic acid precipitate dissolved by alkali before being placed in the Soxhlet tube for bromination. The resultant precipitate has been doubled to give corresponding results.

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