Encephalitis Lethargica.[1] By THOMAS SAXTY GOOD, *O.B.E.*, M.A.Oxon., M.R.C.S., L.R.C.P., Medical Superintendent of Oxford County and City Mental Hospital; Physician-in-Charge, Clinic for Nervous Disorders, Radcliffe Infirmary, Oxford.

ENCEPHALITIS, a disease to be defined as any non-suppurative inflammation of the brain, has been recognized for many years. Crookshank (1) points out that clinical occurrences of the nature of what we now ascribe to encephalo-myelitis and encephalo-meningitis have been recorded for the last 450 years.

In 1918 attention was drawn to the occurrence, in various districts of this country, of a disease to which the name "encephalitis lethargica" was given. This form of encephalitis was characterized by the following:

(1) Epidemic character.

(2) Signs of brain infection by some toxin.

(3) Lethargy varying in degree from slight drowsiness to complete stupor.

(4) Focal symptoms, predominantly motor, the commonest being bilateral, nuclear, and radicular palsies of eye muscles, the third, fourth, fifth and sixth cranial nerves being the most commonly affected, but others also in some cases. Loss of normal facial innervation accompanying the emotions (Parkinson mask). Monoplegias, hemiplegias, diplegias, and choreic and athetoid disturbances. Sensory symptoms implying involvement of the cortex or corona radiata also met with.

Since 1920 various types and sub-types of encephalitis lethargica have been described by such authorities as C. von Economo (2), J. A. Sicard (3), L. Dimitz (4), W. M. Ellis (5), and Hesnard (6). The chief of these types are as follows:

(A) *Hyperkinetic-myelitic type* (C. von Economo).

Onset characterized by neuralgic pains. First stage delirium (often of occupation type, and resembling delirium tremens). Second or hyperkinetic stage, following in a few days, with myoclonia or choreic movements in the abdominal muscles, often one side only. Fibrillary twitchings present. Diaphragm may be involved. Fever persists. Patient often dies at this stage. Third stage, lethargy sets in.

(1) A paper read at a meeting of the Oxford Medical Society on Friday, May 9, 1924.

(B) *Tabetic type* (C. von Economo).

Sluggish reactions, myosis and inequality of the pupils, Argyll-Robertson sign, diminution or loss of knee and Achilles jerks.

(C) *Katatonic stupor type* (Hesnard).

Mental and physical sluggishness, impassivity simulating the clinical features of true katatonia, but often without the waxen flexibility of the latter.

(D) *Psycho-somnolent type* (Hesnard).

Lethargy and somnolence followed by excitement, complicated by hallucinations and mental confusion, with later a tendency to depression and absolute dementia.

(E) *Acute delirious type* (Hesnard).

(F) *Confusional and other psychotic types* (Hesnard).

It should be noted that Hesnard's types, C, D, E, F, do not differ in their physical symptoms from the types of von Economo and other observers, but appear different because of the emphasis that Hesnard lays on what may be termed psychological manifestations.

Many other references could be given, but these will serve to illustrate the point that the disease called encephalitis lethargica may be divided roughly into two main anatomical types: (1) that exhibiting primary lethargy with motor palsies, (2) that exhibiting states of delirium with myoclonic or choreic movements, followed by lethargy. As a temporary convenience I will refer to the former as the lethargic type, and to the latter as the delirious type. The point here raised is: "Are we justified in classifying these two types of encephalitis under the heading *lethargica*, or are there practical and theoretical reasons for distinguishing between them?"

There is no doubt that in many respects the two are alike. Thus, the descriptions of the morbid anatomy of all encephalitis with delirium and encephalitis with lethargy are identical, except that in encephalitis of the acute confusional type the seat of the greatest disorganization is in the cortical area, whilst the morbid change in encephalitis with lethargy is most marked in the stem and bulb and lenticular nuclei. In both types the cerebro-spinal fluid may contain lymphocytes and a trace of albumen in the earlier stages of the disease (7).

I would submit that all the evidence at present produced points to the fact that in both the primarily lethargic and primarily delirious types there is encephalitis. In the lethargic type there is motor inertia; therefore the term "encephalitis lethargica" denotes a primary involvement of the large motor cells of the bulb and stem, and "lethargica" is a fitting term for both the physical and mental

symptoms. But in the other type, delirium, restlessness and motor irregularities are not well defined by the term "lethargica," for the primary clinical symptoms are the exact reverse of what is understood by this term. I submit therefore that the delirious type might perhaps better be designated *encephalitis agitans*, and I venture to make this suggestion because I propose to show that there is some reason for believing that in the early or preliminary stages the two types differ in a very important respect, and are susceptible to different treatment.

I am aware that in venturing to criticize a terminology that has been apparently accepted as adequate by a number of distinguished neurologists, I may be attempting a task which is too great for my capabilities, and that the evidence I bring forward may be insufficiently supported by fact. As, however, my objects are to promote discussion and to try and approach the subject from both a physical and psychological point of view in the hope that some light may be thrown on this serious disease, I will make no further apology, but proceed with my justification for my temerity.

As far as I am aware, the name *lethargica* was first used in the epidemic of 1918. Since that year a large mass of data has been collected, and much research expended to ascertain the nature and cause of the illness. As that epidemic, which was of the lethargic or "sleeping-sickness" type, appears to have given impetus to investigators, it would be natural to expect that attempts to find a pathogenic organism would be greatly stimulated; also, as the physical symptoms in the lethargic type of onset are much more striking than the mental symptoms, it would be natural that a *physical* basis for the disease and a *physical* origin be looked for in its ætiology. That there is a physical basis is not to be denied; but experience, both previous and subsequent to the 1918 outbreak, has shown (*a*) that the disease is not necessarily epidemic, but that cases clinically indistinguishable by their symptoms occur without any epidemic grouping; and (*b*) that while the symptoms are sometimes in their onset primarily motor, in other cases they are primarily psychic. Hence the observer wonders whether, in the causation of the disease, psychological states may not have some bearing from a selective point of view. Is it not possible that, in the confusional types recorded, prolonged mental strain has so affected and weakened the resistive power of the nerve-cells of the cortex, that, on the invasion of the blood-stream by toxins, these cells are most affected because of their exhausted condition or lowered resistance caused by this strain? I personally believe that this is a possibility, and my reasons for this belief I now attempt to set forth.

I wish here to state that I do not consider the evidence I produce in any way conclusive. It is only suggestive, and requires much verification.

In attempting to support this hypothesis, one must take into consideration bacteriological, anatomical, physiological and psychological evidence, and consider carefully clinical experience.

As regards bacteriological findings, I believe these may be condensed as follows: Many observers have verified that the disease encephalitis lethargica is toxic. But, though organisms have been found, none are pathognomonic. A virus has been obtained which has, by inoculation, produced the disease in animals. Sera have been prepared which have apparently beneficial effect when injected in patients suffering from the disease.

I admit to no great knowledge of the science of bacteriology, and therefore my data may be incomplete, but so far as I know, no one has yet discovered why in different cases different areas of the brain are affected. The anatomy of the blood and lymph circulation may be a factor in determining localization, but it is difficult to understand how, when these circulations are affected by a toxin, their anatomy can limit that toxin to a given area unless that area had its resistance lowered by some other factor.

I believe that factor is to be found in the brain-cells themselves, and that in certain cells a bio-chemical change is produced by combined physiological and psychological stimuli. These changes lower the resistance in certain brain-cells of the cortex, and predispose this area to attack by the toxin.

I consider that my hypothesis is supported by the following data:

Tredgold (8) states in regard to nerve-cells of the brain cortex: "As compared with the nerve-cells of the healthy brain, those of the ament are characterized by the following conditions: (1) Numerical deficiency, (2) irregular arrangement, (3) imperfect development of individual cells; and on the whole it may be stated that the amount of change discoverable by the microscope is directly proportionate to the degree of mental deficiency present during life."

Bolton (9) comes to the conclusion that "the cellular elements throughout the cortex cerebri which are specially concerned in the performance of associational functions are those of the pyramidal layer of the nerve-cells; the great anterior centre of association of Flechsig in the prefrontal regions is under-developed, on the one hand, in all grades of primary mental deficiency, and, on the other, undergoes primary atrophy *pari passu* with the development of dementia. This region of the cerebrum is therefore concerned

with the performance of the highest co-ordinating and associational processes of mind."

Both these authorities, therefore, consider that the cortical layer of the pyramidal cells has definite psychic functions. This opinion is supported by others. In a recent paper by Henry Cotton (10), great emphasis is laid on the toxæmic factor in the functional psychoses. In fact he includes manic-depressive insanity, dementia præcox, paranoid condition, psycho-neuroses and toxic psychoses as disorders which are due, in his opinion, to various forms of chronic sepsis. As he includes toxic psychoses, and as acute confusion is a psychic manifestation of one form of encephalitis, he therefore implies that acute psychoses may be caused by a chronic sepsis. Cotton does not appear, from the general trend of his paper, to believe that psychological methods can in any way alleviate or improve these conditions, though he admits that "if any factor, either psychical or mental, becomes operative in the mechanism whereby the immunity is lowered, the infection immediately becomes more active and virulent." Thus by admitted mental factors this latter statement would appear rather contradictory to the general attitude of his paper, for if mental (emotional) factors lower the immunity, it seems to follow that the removal of mental factors must increase it. The point I wish to emphasize here is that although Cotton does not appear to attach great importance to psychological manifestations as having much bearing from a treatment point of view, still he admits in his paper that the mental factor becoming operative lowers the immunity. This admission would appear to support my argument that there are two factors to be considered—one the psychological, and the other the physical. He over-emphasizes the physical, but admits both. Personally, I believe that it is only by giving equal attention to both sides of the question that we can possibly hope to arrive at any solution to some of our difficulties. Cotton's paper does not appear to controvert Tredgold's and Bolton's hypothesis, as they only state that in their opinion certain cell elements have psychic functions, and if their contention is correct, it appears allowable to deduce two facts, namely, that in amentia there are fewer cortical cells, and that in confusional states and dementia these cells are markedly diseased. Admitting, then, that cortical cells have a mental function, we are forced to believe that they must be affected by mental stimuli (emotions) (2), and that these emotional stimuli in their action must cause changes in the chromatic part of the cell. It follows that the cell will become exhausted in proportion to the strength and duration of the stimuli. That the cortical layer has control over the deeper cells is an accepted fact, and if we can

admit that these controlling cortical cells have mental activities, then it becomes a fact also that if these cells are disorganized in their function, their disordered condition would be shown by (*a*) alterations in mentality, (*b*) lack of control over the motor elements.

That alterations in mentality are associated with degenerative or developmental cellular anomalies in the cortex is proved in all cases dying with mental symptoms. Thus, tabo-paresis (*i.e.*, chronic encephalitis due to syphilis) shows marked cellular changes in the cortical layer. Again, the clinical symptoms of confusional states of an acute nature have already been discussed, and I have attempted to show that here also the psychic confusional symptoms are due to cellular changes. Thus mental confusion must always be associated with cellular changes (chromatic elements). It must follow, if this statement is correct, that confusion will subside as and if the cells recover, and it is generally recognized that in the cell the chromatic elements *can* be replaced unless the nucleus is destroyed. As confusion is always accompanied by some degree of encephalitis, and as it is an accepted fact that the cortex cells control the deeper layers, or, in other words, that motor movements are directed and controlled by mind, one would expect that movement would be affected by disordered function of the upper controlling elements. Therefore it is understandable why deliria are invariably accompanied by restlessness. In other words, the discharge from the motor cells is continuous until the cell, because uncontrolled, becomes exhausted; and further, the movements are more pronounced in proportion to the disease or degeneration of the upper elements. Moreover, the stuporose torpor is accounted for by disease of the deeper cells, and probably is also to some extent indicative of the amount of disease present.

Further points that should be borne in mind in considering the functions of the cells of the different layers of the brain are:

1. Bevan Lewis (11) found neuroblastic cells in the second and third layers of the cerebral cortex of the ape. These cells appear to be no different in a morphological sense from the cells described by Tredgold in cases of amentia.

2. Levi (12) found karyokinesis in the small and medium pyramids in the cortex of the guinea-pig. He could not find it in the very highly differentiated cell of the cord and brain, such as the large motor cells. He states he has never observed complete karyokinesis, though he considers it can occur. He thinks that very highly differentiated nerve-cells when affected by a stimulus undergo degeneration instead of attempting to multiply.

These two points further emphasize (*a*) the probability that one great function of the smaller and middle pyramids is mind, and (*b*) that these cells do apparently have a higher potentiality to recover than the more differentiated motor cells. The points that have now been brought forward are the historical and the clinical types of the disease, and the question as to whether the disease is always rightly described by the term "encephalitis lethargica." Certain evidence has been produced from the anatomical, physiological, psychological and clinical aspects to support the following hypotheses:

(1) That there are two main types of toxæmic encephalitis, characterized by different mental and bodily symptoms; and that these symptoms are the signs of the different areas of the brain involved.

(2) That in both types the toxæmic theory is the correct one, and that therefore, from a bacteriological point of view, the disease is the same, but is influenced selectively by changes in cell metabolism.

(3) That though each type may at the onset be localized in its own characteristic area, yet, if the disease persists, all parts of the brain will be affected.

(4) That if the hypothesis of two distinct types of encephalitis lethargica is borne out by facts, it is important for the physician to attempt to form an opinion from the symptoms (3) as to which area of the brain is involved, and this for the following reasons:

(*a*) *From the prophylactic point of view:* If we find that in the confusional type there is always a prolonged period of worry and anxiety (usually due to difficulties in regard to money, or to sex in the widest meaning of the term), then it ought to be possible to treat these cases in the earliest stages by combined psychological and physical means in such a way as to prevent the delirious type from developing. For once it has developed, it is usually necessary to certify the patient.

(*b*) *From a social point of view* it is worth while to do all that is possible to prevent certification, for, do what we will, certification leaves a permanent social stigma. It is rarely necessary to certify the lethargic type, but if the symptoms peculiar to the onset of the delirious type were well recognized, a great deal might be done to prevent its reaching a certifiable stage.

(*c*) *From the point of view of treatment*, if the delirious type is clearly recognized as a distinct variant, due very

possibly to exhaustion of cortical cells brought about by anxiety, then sedatives powerful enough to give complete rest to these brain-cells are of value; for they will not only give the cortical cells a chance to recover, but they will act on the lower cells indirectly through the upper cells, and check motor symptoms.

Having put forth certain theories, and attempted to support them by adducing evidence culled from the work of other neurologists, I wish now in conclusion to put before you the results of some of my own clinical and laboratory experience as a psychiatrist.

It is important to investigate the mental and physical histories of the patients who come before us, for the reason that one would expect to find that in cases of encephalitis with lethargy, physical factors such as bodily fatigue and physical trauma would predominate, and that the mental life of the patient would at the onset be little or not at all affected. As the symptoms, except the drowsiness, are mainly physical, one would expect the physical causation to preponderate, whereas in the onset of the delirious type the mental factors would be more prominent, and one would find in the patient's history certain psychological factors of an unpleasant nature, which have tended to predispose from a selective point the future development of the disease if the invasion of the toxin occurs. I think perhaps a short account of four recent cases will illustrate this point:

CASE 1.—*Boy, æt.* 14½ (*lethargic type*).

Past history.—Had been a normal, healthy boy till five weeks ago; always at work, cheerful. Five weeks ago became drowsy, always falling asleep or dozing, could not do his work, complained of seeing things, saw double, but was, according to friends, quite normal if roused. Only seemed slow and lacking in interest.

Examination.—Boy well developed. Had a fixed smile, and face did not alter much even when an emotion was aroused. This most marked when he was told he had better be admitted to hospital as he was ill. Tears came into his eyes; he said he did not want to leave home; but although he was reasonable, and came quietly into hospital on explanation that he was ill, the "silly smile" was still present, and his face otherwise remained expressionless. Pupils sluggish, rather dilated, and the right rather larger. He had diplopia and some ptosis, slight right facial paresis. No Rhombergism. Tongue protruded slightly to right. Left arm and leg distinctly weaker than right. Deep reflexes brisk. Plantar left was indefinite. Right flexor. Oppenheimer left once extensor, but could afterwards get no response. Right no response. Abdominals normal. Mentally drowsy, slow, but quite coherent and no signs of any confusion. Complained of head feeling heavy. Had a severe cold just before onset.

CASE 2.—*Woman, æt.* 36 (*lethargic type*).

History.—Two months previously had had influenza. By her own statement had seen no doctor at the time, but kept about. Had dull headache; could hardly keep awake. Saw badly, *i.e.*, mistily and occasionally double; noticed nothing more. Was able to keep at work till two months later, but lacked energy and felt ill. Two months ago noticed that her left arm and leg had become weak, especially in lifting anything and in using her wrist. Her toe caught in slight obstructions on the ground. Said that her left shoulder was wasted. Had no worry.

Examination.—Quite collected. Looked heavy about the eyes. Face looked emotionless; pupils slightly dilated, diplopia on rotation to left. Tongue deviated

slightly to left. There was weakness of left shoulder, which dropped slightly, and some wasting of the shoulder girdle. Trapezius, deltoid, supra- and infra-spinatus muscles affected. There was weakness generally of the arm, deep reflexes were present, and there was reaction in the biceps jerk on tapping the wrist tendons. The reflexes in the leg were increased. No clonus, but Babinski present on this side and Oppenheimer. The left arm and leg appeared normal. The electrical reactions of the wasted muscles were reported as normal. There appeared no alteration in mentality.

CASE 3.—*Boy, æt.* 17½ (*delirious type*).

History.—Had been worrying over school responsibilities. Sexual problems of puberty. Was said to have been delicate as a child and at first had not been allowed to play games, though afterwards developed in this direction. Was always thought "rather nervous." Two months ago had influenza; was ill for about three weeks. Recovered, then had slight attack which was designated acute neurasthenia, when he appeared worried, and is said to have stated he was a failure. Rapidly recovered, and then appeared quite normal except that he was for a time excited and unduly talkative and restless. About a week before present attack broke out into an erythematous rash (diagnosed as German measles). Seemed to have recovered, but began worrying and became confused at times. Before out of quarantine this confusion rapidly increased. Marked insomnia, great motor restlessness and continual repetition that he was to blame—that it was all his own fault.

Examination.—When examined showed the greatest confusion; could not be kept to one subject for more than a few moments. Appeared to recognize people momentarily, but rapidly became delirious and confused, constantly repeating, "Yes, that is so; I must find out." The pupils were widely dilated and sluggish. There was uniform and almost continuous myoclonic spasm of right arm and leg. The restlessness was so great that reflexes could not be tested.

CASE 4.—*Man, æt.* 28, *undergraduate* (*delirious type*).

History.—Had had a nervous attack when 14. Had been through the war. Had matured. Had been worrying over money matters, and also had a phobia about dirt. Ten days previously had influenza, followed by abortive attack which appeared to be apical pneumonia. Was normal mentally till the pneumonia began to subside, when he suddenly became delirious.

Examination.—The delirium was very confusional, and appeared always after sleep, which was only obtained by drugs. He was intensely restless. Pupils sluggish, had complained of headache and misty vision. Reflexes were normal, no signs of rigidity or paresis. There had been great constipation. Patient's attention could be held for a certain period, but the confusion returned if attention was distracted.

These four cases, which were seen within one week, had no previous contagious history, but all had influenza. All, in my opinion, were cases of encephalitis. Two were of the lethargic type, two of the delirious and confusional. In the lethargic cases mental history had no obvious bearing. In both confusional cases there was a positive history of emotional stress. In my experience all confusional states have this history of emotional repression, usually in connection with money or sexual matters.

POST-MORTEM FINDINGS.

All the cases dying of encephalitis which have come under my personal notice have been of the delirious confusional type, with intense motor restlessness, with or without choreic or myoclonic movements. The *post-mortem* findings have been as follows:

Pia arachnoid slightly milky, with in some cases a certain bulbous œdema along the edges of the longitudinal fissure; in one case the bullæ were large and contained

clear yellow serum. The brain generally was bright pink in colour, with petechial hæmorrhages and general engorgement. Microscopic examination showed engorged, thrombosed and hyaline vessels and migration of endothelial cells, the lymph-spaces of vessels containing many endothelial or lymphoid cells. These were present also in the brain substance, in the pericellar lymph-spaces, and in many cases had invaded the nerve-cells themselves, Nissl bodies being disintegrated, dentrites degenerated. Nuclei and nucleoli in many instances were either degenerated or had disappeared, the cells that once contained them being of the "ghost type." The method of staining was Ford Robertson's methyl violet and Missl's toluidin blue. The sections were usually taken from the apex of the ascending frontal convolutions, though other regions of the brain were examined. In only one case was bacteriological examination made, and in this case no micro-organism was found. At the meeting of this society last year two sections of the cortex were shown in which there was marked encephalitis of this confusional type. One was apparently secondary to tubercular meningitis, whilst the other showed no definite meningeal infection; but the cortical encephalitic lesions were well marked in both cases, especially in the smaller and medium pyramids. In both these cases there had been clinically intense motor restlessness, confusion, slight hemiplegic attacks and ocular symptoms.

I have at this hospital recognized only one case of the lethargic type of this illness, but it is highly probable that cases occurred and were missed previous to 1918. I had, however, recognized and examined cases of the delirious type previous to that date. It is probable in a hospital dealing with mental disorders that the drowsy type is seldom admitted in the earlier stage, for the reason that the lethargy is diagnosed as illness, and as the patients are quiet, nobody thinks them insane, whereas in the delirious onset the mental confusion often associated with hallucinations is alarming to both relatives and medical men, and the case is certified at once. All very sudden attacks are probably of the delirious nature.

To sum up, the truth about encephalitis appears to be that it is due to an acute toxæmia. The selective factor may be either physical or psychological stresses. It is only by careful investigation by every method, both physical and psychological, that we can hope to arrive at a correct interpretation of the values of the predisposing factors—that is to say, combined team work is essential in our investigations. In the past there has been too much severance between the investigators at the general hospital and the mental hospital. As the training of the medical profession has been in the past mainly along physical lines, the trend of investigation has naturally been predominantly physical, and therefore, though mind has been accepted as existing as part of the general make-up of the individual, it is only quite recently that the workings of the mind have been studied with what one might term a psychological technique. The adherents of this technique have, perhaps, by over-emphasizing their theories, brought upon themselves and their methods a certain measure of incredulity and opprobrium such as is often caused by the over-enthusiasm of the adherents of any new method.

The ultimate solution of the problem of psycho-neuroses and psychoses is only to be found by investigating their manifold phenomena by both psychological and physical technique, and if in this paper I have been able to throw any light on the disease of encephalitis by dividing it according to the predominantly physical or predominantly mental manifestations into two types, and if I have established my hypothesis that emotional stresses are the predisposing factors in the confusional type, it is a proof that defective ideation, which is confusion, always accompanies as a symptom, and is always diagnostic of, the pathological changes in the cortical cells, and that the cause of the predisposing factor is often, if not always, to be found in the individual failure of the patient to adapt his or her mental feelings (emotions) to environment. As confusion implies an intellectual defect, and as intellect is different mental stuff from emotions (mental feelings), the fact that confusion is caused by disease of the cortical area tends to prove that intellectual faculties are a property of the cells in the cortex of the brain. As insanity is a failure of the individual to adjust to the environment, and may show either predominantly intellectual disability, or emotional instability without any intellectual dulling, intellectual insanity is a sign of disease of the nerve-cells which are a definite part of the organism, while emotional abnormalities, which may exist without any evidence of the intellect being impaired, do not appear to be able to be located in any definite region at present.

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(11) Lewis, Bevan.—*Text-book of Mental Diseases*, 1899, and *Brain*, October, 1879.
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(2) Some may not admit that an emotion is primarily a mental process, but no one will deny that the effect of an emotion will cause bodily changes in metabolism. The simple examples of a blush, sweat of fear, vomiting of horror are well known.
(3) The points of value in diagnosis are the confusion and restlessness of the patient, whereas the depression or exaltation is of no diagnostic significance.