A Lecture ON ENCEPHALITIS LETHARGICA IN ENGLAND.*

BY

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ENCEPHALITIS LETHARGICA, or epidemic encephalitis, which may be classed under the head of general infectious diseases, is distinguished by certain manifestations originating in the central nervous system. One of the most characteristic of these manifestations is due to a lesion in or about the nuclei of the third pair of cranial nerves. The progressive lethargy and stupor which are often present caused von Economo[1] to give the descriptive term "lethargica" to the disease. The name "sleepy sickness," which, for the same reason, is sometimes popularly used, is to be deprecated, as it is apt to lead to confusion with the sleeping sickness of African countries—an entirely different malady due to a trypanosome.

HISTORY OF THE DISEASE.

1. *Past Appearances of Encephalitis Lethargica.*

Crookshank[2] has pointed out that scattered through the medical literature of the last four or five centuries are many records of cases and epidemics that may possibly correspond to the various types of encephalitis lethargica now recognized. Some of these outbreaks are ascribed to food poisoning; others are associated with catarrhal epidemics which were probably influenzal. For practical purposes the disease is a new phenomenon.

2. *Appearance of Encephalitis Lethargica in England.*

Encephalitis lethargica was first recognized in this country in 1918, when an outbreak simulating food poisoning occurred in the spring of that year. A notable feature of the outbreak was its wide and sparse distribution. From careful investigation instituted by the Local Government Board, with the collaboration of the Medical Research Council, the malady was recognized as a distinct clinical entity and later found to be identical with that described in the previous year by von Economo and von Wiesner in Austria. The clinical characters of the disease and the features which distinguish it from such closely allied conditions as acute poliomyelitis and polio-encephalitis are described in detail in the two official reports on the subject which have been published by the central health authority.†

PATHOLOGY AND ETIOLOGY.

The pathological histology of the disease consists in the main of a perivascular cellular infiltration of lymphocytes with occasional plasma cells in scattered areas of the central nervous system. For this no visible parasitic cause (for example, bacteria, protozoa) can be found. The distribution throughout the central nervous system is uneven. The sites of election are the region of the nuclei of the third nerve and the basal ganglia, but other areas may be attacked.

The cerebro-spinal fluid shows a slight increase in the total protein content and an increase in the number of cells (lymphocytes with occasional plasma cells) per cubic millimetre.

Various observers (McIntosh,[3] Levaditi,[4] Doerr,[5] etc.), by inoculating a virus obtained from human cases, have provoked in rabbits and monkeys brain lesions indistinguishable from those characteristic of encephalitis lethargica. Levaditi,[4] Perdrau,[6] and others find that a virus obtainable from the vesicles of herpes febrilis (not herpes zoster) used in the same way produces the same results. Much further experimental work is needed, and is being actively conducted in this country and abroad.

In the Milroy Lectures for 1925[7] I have considered certain possible explanations, not necessarily incompatible, that may be advanced on the subject of an apparently increased, and rapidly increasing, susceptibility of the central nervous system to attacks of epidemic nervous diseases, including encephalitis lethargica.

CHIEF CLINICAL FEATURES.

The disease attacks all ages, with a preference for the early and middle periods of life, and both sexes nearly equally.

From the clinical point of view three types are distinguished: (1) general disturbance of the functions of the central nervous system but without localization; (2) various localizations in the central nervous system; (3) mild or so-called abortive cases.

After a period of incubation, the duration of which cannot at present be specified, a prodromal period ensues; this includes the first seven days, but may extend to two or three weeks, during which lethargic somnolence, headache, double vision, general lassitude, and occasionally vomiting and diarrhoea, may occur. Soreness or dryness of the throat may also be present. The acute symptoms which follow include a febrile temperature (101° to 102° F. = 38.3° to 38.8° C.), marked asthenia, stupor (alternating often with nocturnal delirium), difficulties in speech, and spasmodic twitchings of the face and limbs. Skin eruptions are occasionally noted. There is no characteristic rash; an erythema is most often seen, but the eruption may be petechial, papular, morbilliform, or scarlatiniform. The rashes when present appear early in the disease and during the pyrexial period. They are transient, fading in twenty-four hours as a rule. In the type of the disease with localizations in the central nervous system paralysis of accommodation with diplopia is very frequent and occurs early. There may be ophthalmoplegia, external or internal, with ptosis. The muscles innervated by the facial nerve may also be paralysed as well as the muscles of the tongue, pharynx, etc., rarely those of the limbs. The paralysis is progressive in character. Sensory troubles are the exception. There is often urinary or faecal incontinence and sometimes retention of urine. Death appears due to paralysis of the respiratory nervous centres. It is preceded by an increase in delirium and stupor merging into coma. It occurs most frequently before the end of the third week.

The severest cases lie in bed like a log or resemble a waxen image in the lack of expression and of mobility. The immobility may be accompanied by catalepsy. Various degrees of stupor have been noted. The condition may be one of deep coma, with open eyes, total lack of facial expression, and inability to be roused. More commonly the condition is not so grave, but the patients are in a profound sleep, from which they can be aroused to answer questions or to partake of food. When undisturbed they quickly lapse again into stupor. Certain patients resent being roused and display intense irritability or utter moaning cries when touched. The duration of the stupor is very variable. It may last for only two or three days, or more often may persist for two to five or even eight weeks. Periods of remission may occur in the course of the malady. The onset of coma, although grave, does not always imply a fatal issue. Many patients display extreme emotion and are "childish" in demeanour.

It may be mentioned that the clinical type of case seen during the present period of prevalence (1924-25) appears, on the whole, to be less severe than the above description, which is based on the study of cases seen in preceding years. In many instances the prodromal period appears to exceed the usual seven days. The onset is often ascribed to "influenza," and a fortnight or more elapses before the definite signs of encephalitis are manifest. Patients do not remain for lengthy periods in profound stupor or

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† (1) Report of an Inquiry into an Obscure Disease, Encephalitis Lethargica: Reports to the Local Government Board on Public Health and Medical Subjects, N.S., No. 121, London, 1918. (2) Ministry of Health Report on Encephalitis Lethargica: Reports on Public Health and Medical Subjects, No. 11, London, 1922.

coma, and some have made an unusually rapid recovery; catalepsy is rare.

While the prominent symptoms in a material proportion of cases remain those of lethargy and ocular paralyses, many are chiefly characterized by myoclonic movements and sometimes by fibrillary twitchings of the abdominal muscles. Affections of the cortex of the brain are more frequently seen than in previous outbreaks; these are characterized by epileptiform convulsions and are sometimes associated with maniacal outbursts or insomnia.

EPIDEMIOLOGY.

1. *Incidence.*

Encephalitis lethargica was made compulsorily notifiable in England and Wales on January 1st, 1919, and from that date fairly complete records of all recognized cases are available. The number of cases of encephalitis lethargica notified in 1924 was 5,039. This number exceeds the sum of all the notification tables for the preceding five years, as may be seen from the following table.

England and Wales: Notifications and Deaths from Encephalitis Lethargica since this Disease became Generally Notifiable.

Year.	Notified Cases.	Deaths.
1919	541	264
1920	890	471
1921	1,470	724
1922	454	337
1923	1,025	530
1924	5,039	1,419

There was an unusual prevalence also in Scotland and Ireland in 1924.

2. *Incidence in Urban and Rural Communities.*

Encephalitis lethargica has been reported chiefly from urban districts. In 1924 the rural districts only contributed 12.8 per cent. of the total number of cases, while the county boroughs alone were responsible for 46.6 per cent. Large cities and industrial centres have been particularly affected, probably on account of the enhanced opportunities for the spread of personal infection, although possibly the better facilities for medical diagnosis possessed by large towns may also be a contributing factor. In 1918 I found a restricted topographical distribution of cases of encephalitis lethargica in certain districts, notably in the county borough of Stoke-on-Trent. The same tendency for examples of the disease to clump in certain areas of a town or city was noted in 1924 in Sheffield, Bristol, and elsewhere, probably associated with density of population and increased opportunities for case-to-case infection. Parsons has found in Bristol and elsewhere that this topographical grouping in towns tends to be the same in different epidemic years—a circumstance which suggests the presence of endemic foci of the disease.

3. *Mortality.*

In 1918, in the first outbreak in this country, out of 168 cases of the disease 37 died—a case mortality of 22 per cent. Variant case mortality rates are quoted by Parsons, ranging from 53 per cent. (McClure) to 15.7 per cent. (Bramwell). The notification figures (England and Wales) for 1919-23 gave a case mortality rate of 54 per cent. In view of the failure to notify cases of epidemic nervous disease generally, and through failure to recognize mild non-fatal types of encephalitis lethargica, these figures cannot be taken as a true estimate of the number of deaths that occur among persons attacked by encephalitis lethargica. No definite opinion can be expressed at present as to the case mortality, except that it is probably under 50 per cent.

4. *Age and Sex.*

All ages may be attacked, from the newborn babe to the octogenarian. A woman of 84 has died from the disease. The main incidence of the disease begins to be apparent in those approaching adult life; 25 per cent. of a series of British cases occurred in persons between the ages of 10 and 20 years. The incidence appears to be fairly evenly distributed over the years 20 to 40, but the tendency to acquire encephalitis lethargica declines with advancing age. The records of the Ministry of Health show that the sexes are equally affected. Of 1,273 cases, 634 were males and 639 females. This proportion is evenly maintained at different age periods.

5. *Seasonal Prevalence.*

The first outbreak occurred during the first quarter of 1918. James early called attention to the difference between the seasonal incidence of the disease and that of poliomyelitis. Since then the increase in the number of cases in the colder months of the year has been annually noted in this country, the rest of Europe, and in North America. The increase in the incidence of encephalitis lethargica usually begins towards the end of December and continues during the first quarter of the new year. The second quarter also shows many cases, but by the end of May the epidemic has waned and many fewer cases, as a rule, are notified in the third and fourth quarters of the year.

6. *Predisposing Causes.*

Careful inquiries have been made by the Ministry of Health into possible predisposing causes, but little of value has resulted from the quest. The influence of pregnancy is regarded as of importance by some writers. Jorge,[8] in reviewing a series of 18 pregnant cases, found that the mortality rate was 72 per cent. On the other hand, the Ministry's figures show that the mortality rate in respect of all the cases of encephalitis lethargica which were associated with a pregnancy, past or present, is 44 per cent.; this percentage also represents the general case mortality among all women between the ages of 20 and 40 who contracted the disease during 1919 and 1920. Social conditions appear to exert no influence upon the disease. As regards occupation, from a study of 1,070 patients, Parsons found that 734 followed indoor occupations, 133 engaged in outdoor occupations, while 203 patients belonged to an indeterminate group. He concludes that the disease chiefly attacks those who spend the greater part of the day indoors in pursuit of their avocations. Overwork is often assigned as a predisposing cause. The specific infectious diseases and diseases generally do not appear to dispose to the disease beyond the circumstance that any antecedent or associated disease may lower the patient's resisting powers to infection.

EVIDENCE FOR REGARDING ENCEPHALITIS LETHARGICA AS AN EPIDEMIC DISEASE.

The epidemiological evidence already available in regard to cerebro-spinal fever and acute poliomyelitis greatly facilitates an understanding of the behaviour of encephalitis lethargica. No evidence has been elicited that the virus of this disease is conveyed through intermediate agencies, such as water, soil, food, clothing, biting insects and flies, etc. The chief facts relating to the spread of encephalitis lethargica by personal contagion are as follows:

(1) The restricted topographical distribution of cases to which allusion has been previously made.

(2) The cases reported by Harris, Kononowa, Novaes and Sousa, and others, of infection *in utero* or placental transmission.

(3) The examples of multiple cases in families and localized outbreaks in small communities.

(4) Examples of case-to-case infection, where infection from a common source was apparently excluded.

Dr. Parsons and I have put on record in official reports several examples of multiple cases of encephalitis lethargica in families, and Netter[9] has reported a number of similar instances in France.

An interesting example is that communicated by Van Boeckel[10] at Ruddervoorde, in West Flanders, in 1919, where the disease attacked four families who were closely interrelated. Of 26 persons, 17 were attacked, and 4 of these died. Kling and Liljenquist[11] of Stockholm found, in February, 1921, that encephalitis lethargica was prevalent in certain villages in Lapland, the morbidity rate varying from 7.1 to 45 per cent. In some families several members contracted the disease simultaneously,

and in two houses almost all the inhabitants were affected. Side by side with the severe and typical cases were catarrhal and febrile cases, cases with slight affection of the ocular movements, and a few cases of obstinate hiccup.

In the Annual Report of the Chief Medical Officer of the Ministry of Health for 1919-20[12] I recorded an institutional outbreak of encephalitis lethargica in a home for girls at Derby: 12 persons were attacked out of 22 inmates, and there were 5 deaths. John and Stockebrand[13] have reported a similar outbreak in an asylum at Mulheim in the summer of 1922. Here 28 cases with 13 deaths occurred in twenty days, 6 being in nurses and 2 in doctors. Dysphagia and ophthalmoplegia were frequent symptoms.

It is known that mild and ambulant cases of illness exist in association with declared cases of encephalitis lethargica; several instances of the kind were encountered in 1924 in Liverpool, Sheffield, and elsewhere; through their medium the conveyance of infection from one person to another seems to be more than probable. I would suggest that the presence of these "carriers" in encephalitis lethargica indicates that the disease is in accord with cerebro-spinal fever and poliomyelitis as one in which the pathogenic agent is more frequently present in the human organism than the clinical evidence would imply. The work of Eastwood, F. Griffith, and Scott[14] has already established this conception as true for cerebro-spinal fever. Encephalitis lethargica appears to be equally infective and liable to manifestation in epidemic form.

The Question of Reinfection.

It is impossible at present to say whether the disease may occur more than once in the same individual. Netter,[15] G. E. Price,[16] and Buzzard[17] have recorded cases in which patients have apparently recovered and eventually have succumbed to encephalitis lethargica. On the other hand, the frequent occurrence of sequelae, mental changes, symptomatic paralysis agitans, and the like, may be due to persistence of the virus of the disease, which, like the virus of syphilis, may be capable of lurking quiescent in the body for long periods and of returning to activity from time to time.

Route of Infection.

Like cerebro-spinal fever and acute poliomyelitis, it seems a fair assumption that the virus of encephalitis lethargica first infects the upper respiratory passages, where it may either lurk and give rise to the carrier phase in the person affected or may pass on to attack the brain. There is no definite catarrhal stage associated with its early manifestations, but sore throat is a frequent concomitant. There is reason to believe, in view of the frequency of initial conjunctivitis, that the virus may enter the brain through the eyes; infection by the gastro-intestinal route is also a possibility.

Epidemic Hiccup.

Sir John Robertson, medical officer of health for Birmingham, from his experience in the Birmingham epidemic of 1924 is strongly of opinion that epidemic hiccup may be a symptom of encephalitis of a mild type. The disease has been seen in definite association, for instance, in the same household with encephalitis lethargica; an attack of hiccup may precede or accompany the nervous symptoms of the major disease, and there is good reason, in view of the cumulative evidence, for regarding epidemic hiccup as a mild or frustrated form of encephalitis lethargica.

Chronic Encephalitis Lethargica or Sequelae of the Acute Form.

The sequelae are both of neurological and medico-legal importance. They may appear (1) in the course of the original acute malady and persist after partial or complete disappearance of all other symptoms, or (2) after the original acute attack has apparently terminated or possibly has passed unrecognized. Such effects are declared after a variable latent period ranging from some weeks to over two years. No definite opinion, therefore, can be expressed until after some years as to whether an attack of acute encephalitis, however mild in appearance, may or may not result in serious sequelae. The more important of these after-effects are:

1. *Mental Symptoms.*—In all probability these are dependent upon lesions of the cortex of the brain. Irritability, maniacal outbursts, hebetude, complete change in moral character and self-control, lying and theft, may appear for the first time in the conduct of the victim of encephalitis lethargica, as well as grosser mental defects (including even homicidal attacks) which result in the patient's transference to a mental institution. These symptoms are of all grades of severity and may be associated with nervous lesions. They are usually seen in children or in the young adult.

2. *The Parkinsonian Syndrome.*—This condition closely resembles and may be identical with paralysis agitans as seen in the elderly or middle-aged adult. Fewer cases of disease are more pathetic than juvenile examples of this condition, and alike in children and adults it must be regarded as one of the gravest sequelae.

3. *Excito-motor Sequelae.*—Myoclonus: sudden, shock-like muscular spasms of limbs, sometimes also of diaphragm and larynx. Halting and slowed movements (bradykinesia).

4. *Other Sequelae.*—Of these, increased tone of muscles, paralysis, various sensory symptoms, and curious respiratory spasms (polypnoea, periods of apnoea, Cheyne-Stokes respiration) may be mentioned.

It is as yet unknown whether these manifestations are true after-effects or if they are indicative of persistence of the original infection. It is impossible also, at present, to say what proportion of surviving cases of encephalitis lethargica exhibit after-effects, whether mental or physical. Investigations are now being made on this question. It appears to be probable that mental after-effects, especially in children, occur in a large proportion of the surviving cases. Of the seven survivors of the Derby outbreak, two subsequently developed mental symptoms.

Prevention and Treatment.

As advised in the memorandum of the Ministry of Health, the medical officer of health faced with an outbreak of encephalitis lethargica in his district should pursue the following lines of action:

(*a*) Full determination of the associated conditions and any facts which may throw light on the epidemiology of the disease.

(*b*) Search for mild and abortive cases.

(*c*) Aiding in any practicable pathological investigation and in obtaining material for the purpose.

(*d*) Aiding in securing the treatment of the disease in hospital or otherwise.

(*e*) Enjoining the precautions required in the case of a disease apparently capable of transmission from person to person, especially through mild and abortive cases capable of carrying infection; and

(*f*) "Following up" and recording the after-history of patients; in particular, as to any mental after-effects which may be observed. In this connexion inquiry should also be made into the previous history of children who begin to exhibit changes in behaviour or unusual accentuation of undesirable qualities; these symptoms not infrequently point to an overlooked attack of epidemic encephalitis at an earlier date.

In view of the severity of the disease and the importance of good nursing, it is important to secure hospital treatment as far as possible. The isolation hospitals of local authorities should be available for this purpose; at the same time a number of cases may have to be treated in their own homes; for these public nursing facilities, possessed by or arranged with the authority, should be available. The other occupants of a house in which a case of encephalitis lethargica has occurred or is being treated may be assured that owing to variations in individual susceptibility the disease is one of low infectivity, and that slight risk, as a rule, is run by association with the patient. It is desirable that such association should be limited to the necessities of proper care and nursing, and the patient should be well isolated in a separate room. School children in the affected household may be kept from school for three weeks after the isolation of the patient as a precautionary measure. There is

no necessity to place restriction on the movements of other occupants provided they are frequently examined and remain well. Those in contact with the case may be advised to use antiseptic nasal sprays, douches, and throat gargles. Any persons in the infected household who suffer from sore throat or other symptoms suggestive of an abortive attack should be medically treated and isolated until they have recovered. The sick-room should be thoroughly cleansed and disinfected at the end of the illness.

Although there is no specific treatment, much may be done to sustain and tide the patient over the acute period of attack. Confinement to bed, the services of a trained nurse, and treatment as an infectious disorder are primary essentials. In many cases transient or permanent relief with diminution of stupor follows on the withdrawal of cerebro-spinal fluid by lumbar puncture. It is seldom advisable to administer hypnotics, morphine, or other preparation of opium; urotropine, if prescribed, should be administered in small doses with caution and with suitable tests as a guide. Hall advises belladonna in the treatment of chronic forms of the disease.

CONCLUSION.

To encephalitis lethargica we may apply the words of Harvey: "Nature is nowhere accustomed more openly to display her secret mysteries than in cases where she shows traces of her workings apart from the beaten path; nor is there any better way to advance the proper practice of medicine than to give our minds to the discovery of the usual law of nature, by the careful investigation of cases of rarer forms of disease."

The study of encephalitis lethargica has made many problems in neurology and physiology plain; but the existence of this tragical disease in our midst is a heavy price to pay for the acquisition of new learning. Sir Thomas Browne wrote: "Some will allow no diseases to be new, others think that many old ones are ceased; and that such which are esteemed new will have but their time." But even if this last is true of encephalitis lethargica, it behoves us all to endeavour to shorten the time of visitation. You will have gathered from what has been said how serious is the disease and how deplorable and frequent are its after-manifestations.

Further study of the malady will add to our knowledge and will furnish us with fresh weapons for attack and defence. In this crusade the team work of the epidemiologist, the physician, and the pathologist is all-important.

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THE ABSORPTION OF MERCURIALS FROM OINTMENTS APPLIED TO THE SKIN.

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IN two previous papers by one of us[1] an attempt was made to determine the relative values of the different substances used as bases for ointments, both as regards protection and absorption, and it was found that lard and hydrous wool-fat were absorbed more readily than the paraffin bases. We have no information as to whether the drugs combined with these bases to form ointments are absorbed *pari passu* with the base, or whether the bases readily part from the drugs so that the latter may be absorbed either more quickly or more slowly than the base; neither do we know whether a drug dissolved in the base behaves differently from one which is merely mechanically mixed with it. It seemed desirable, therefore, to attempt to determine these points by the method described in the previous papers, but work on these lines was interrupted for some years by the war, and has only recently been completed and the following results obtained with respect to certain mercurial ointments.

The mercurial ointments were selected for study for two reasons: first, because the absorption of mercury through the skin is of importance in regard to its clinical use—in some cases desirable, in others to be avoided; and secondly, because mercury and its compounds can be quantitatively estimated with great accuracy. It was found, however, that the accurate determination of mercury and its compounds when combined with fats or paraffins of various composition presented special problems in analysis and required special methods; these methods were first worked out and the results have already been published by one of us.[2]

The method employed was to make an accurate determination of the mercury in a sample of ointment; a carefully weighed quantity of this was then rubbed into a definite area of skin, about 20 square inches, for a definite time. The unabsorbed ointment was then scraped off the rubbing finger and the surface of the skin by a dulled Gillette safety razor blade fixed in a convenient handle, and again weighed. To avoid the necessity of wiping the instrument the scraper was weighed with the ointment both before and after rubbing. The amount of mercury in the unabsorbed ointment was then determined. The loss of weight represents the amount of ointment absorbed together with that lost by manipulation, and as the latter is fairly constant in dealing with preparations of similar consistence the results afford a relative indication of the respective amounts absorbed. From a comparison of the analysis of the ointment before rubbing with the analysis of the unabsorbed ointment it is easy to calculate the amount of mercury, or mercurial salt, absorbed as well as the amount of base.

It was found, after doing a number of preliminary experiments, that absorption was not so good when the skin was cold—as, for example, in the morning in cold weather. In order, therefore, to reduce the number of variable factors as much as possible the experiments were always carried out in the afternoon, and the skin area was well washed with hot soapy water and thoroughly dried immediately before rubbing. It was also found that the variable thickness and texture of the skin in different parts of the body and in different persons affected the amount absorbed, and the experiments from which any conclusions were drawn were all carried out on the same