Critical Review.

POSTENCEPHALITIC PARKINSONISM AS A CHRONIC INFECTION.

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ACTIVE INFECTION IN PARKINSONISM.

SOME well recognised features of postencephalitic Parkinsonism are of such a nature as to suggest to the clinician a chronicity of the infection in the brain. Among such features are (1) the gradual appearance and often steady progression of the syndrome many months or several years after an acute encephalitic attack, the patient having, perhaps, been quite well in the interim; (2) the insidious development of the syndrome with no history of an acute attack (i.e., the infection being chronic from the first); (3) a certain amount of evidence of contagion long after the commencement of the illness; (4) the appearance and variable course in Parkinsonism of other encephalitic signs and symptoms; (5) the occasional recurrence of the disease in an acute form, perhaps months after the first attack. From the point of view of treatment it is important to deal with this question of active infection. Is it definitely shown that in some, or many, cases, the virus is still active? Can those that are definitely still infected be discriminated from those where the symptoms are truly 'residua'? What is known of the virus and can specific measures be used against it? If not, what results would successful non-specific treatment bring? It is proposed in this review to discuss some of the evidence for and against the view that chronic infection may persist in Parkinsonism and to attempt to answer the above questions.

THE PRESENCE OF CHRONIC INFECTION.

The balance of the evidence and opinions put forward by large numbers of workers is overwhelmingly in favour of a persistence of the infection in many cases of 'post'-encephalitic Parkinsonism. Yet examination of all this work shows that the activity is very low-grade and probably often dies out completely.

Von Economo himself first described a chronic type of case progressing by stages or 'shoves.' Nonne found that there might be an interval of from three to four years' freedom from symptoms between an acute attack and the appearance of sequelæ, e.g., the Parkinsonian syndrome: and a latent period like this of as long as four or five years has frequently been noticed since. Wimmer, commenting on this interval, regards the postulation of a persistent infection in the brain as the best explanation and compares chronic

encephalitis with neurosyphilis, where immunity and activity go hand in hand. However, Ivy Mackenzie is not convinced that insidious development of Parkinsonism is due to extension of the lesions through persistent infection, but regards the appearance of the syndrome as due to a gradual process of functional adaptation of diseased areas of the brain to their altered state. It is difficult to find any convincing physiological support for this theory. Suggestions (Stern, Mourge) have been made that the virus might cause metabolic changes, the effects of the latter producing, with the passage of time, lesions in the basal ganglia, etc. Thus Mourge compared epidemic encephalitis with the encephalitic changes occurring in animals after removing the liver from the circulation by production of an Eck's fistula. Doubtless these suggestions were born in an attempt to find an analogy with progressive lenticular degeneration. They were supported by the finding by the same workers of some signs of liver failure in epidemic encephalitis, e.g., glycosuria, urobilinuria, and impaired laevulose tolerance. There has been no general confirmation of this finding, and to prefer these alternative suggestions to that of a persistent extending infection is to become still more hypothetical.

Post-mortem evidence (regarded by most authorities as conclusive) of active infection in the brain in long-standing cases, including those of Parkinsonism, has been found. Hohman said that a striking feature in his cases was the universal finding of persistent signs of acute and subacute inflammatory reaction, even after months or years of the disease. He found definite areas ("sometimes difficult to detect, but always present") of round-cell infiltration, with plasma-cells and lymphocytes. McAlpine said (1923) that he and many other observers had discovered signs of active disease post-mortem in Parkinsonism, these signs being the presence of inflammatory cellular exudates. Freeman noticed (1) the presence of fat in scavenger cells and (2) collections of small lymphocytes within the sheaths of blood-vessels, and compared the picture with that of general paralysis of the insane, where it means "unequivocally persistent inflammation." Greenfield states that slight cuffing of vessels and small infectious nodules may be found in the most affected areas of the brain. He emphasises the fact that although they have been accepted as signs of persistent infection they are not the most prominent post-mortem feature, which is neuronal decay. He admits the evidence that the virus may linger on in some cases for months or years "in a virulent form" and produce the slowly progressive cases, but thinks that in most the virus dies out completely in a few weeks after the acute attack.

DISCRIMINATION OF CASES WITH ACTIVE CHRONIC INFECTION.

On the above arguments active infection should be regarded as being present if the case at the time of observation is progressive. Thus if a case of Parkinsonism begins by insidiously developing the mask-like facies and some general poverty of movement and if this becomes gradually more pronounced and extrapyramidal rigidity with Parkinsonian posture is slowly

superadded, then during the time that this process is at work active infection is present. However, between an acute attack of encephalitis and the onset of Parkinsonism, a period of up to four or five years may elapse during which the patient may remain perfectly well. All this time the infection is lying dormant and there is nothing that reveals its presence. There is no metabolic change or alteration in the blood-picture or cerebrospinal fluid whereby it may be demonstrated. Therefore, every patient who has once had an attack, with either an acute or an insidious onset, of epidemic encephalitis should be regarded as a case of active disease for several years to follow, and any treatment of the infection that is possible is indicated during this period.

THE VIRUS.

The early attempts of Loewy and Strauss, and Kling, to transmit the virus of encephalitis to animals are to be discounted. The work of Loewy and Strauss and Kling is largely deprived of its value by the discovery by McCartney of the occurrence among stock experimental rabbits in America of an encephalitis due to a parasite—the *encephalitozoon cuniculi*—which may produce in the animal, without giving rise to symptoms, microscopical appearances identical with those described by the former workers and alleged by the latter to have been produced by the encephalitic virus. McCartney found this spontaneous encephalitis of rabbits in 5.0 per cent. of 372 animals whose brains he cut. This corresponds exactly with the percentage of successful transmissions of epidemic encephalitis claimed by Kling. Also, Kling's rabbits did not develop any symptoms of encephalitis but were killed some time, e.g., two months, after having been inoculated with infective material and their brains examined microscopically. Such evidence of transmission of encephalitic virus is ambiguous and unsatisfactory. One point in Kling's favour is that he could not find evidence of parasitic encephalitis among his stock rabbits. Also, McIntosh has recently said that the spontaneous encephalitis of rabbits is distinguishable microscopically from a true transmission of the epidemic encephalitic virus. He is convinced that the latter has been produced and that in it the perivascular cellular exudate is predominantly lymphocytic, whilst in the former it is granulomatous, i.e., composed of endothelial cells. Flexner's criticisms of the early work on the virus may be quoted, and, even if successful transmissions were obtained, the latter tell us nothing of the nature of the virus. An early attempt at cultivation of the latter as visible globoid bodies was shown to be without value.

Flexner, writing in 1920, stated that his efforts to obtain positive transmission of the virus to animals failed completely. He was unable to repeat the successes claimed by Loewy and Strauss. He said that nothing consistent came of the work on monkeys and that only a very few positive results were reported. McIntosh's positive result after keeping his infective material in glycerol for fourteen days, was described as problematical. Criticism was also directed against Levaditi's claims of successful transmission, and against his

views on the nature of the virus. Levaditi succeeded in transmitting to a rabbit a virus that could be passed from animal to animal, and which resembled in its action the virus of herpes febrilis. Both viruses when inoculated intracerebrally, or on the scarified cornea, produced a fatal encephalitis with symptoms. Rabbits could be immunised against either virus by dermal injection and immunity to one virus protected against the other. Much further work has been done on the relation of these two viruses and will be described below. Flexner's criticism was that the so-called encephalitic virus that Levaditi obtained was actually herpes virus itself, an accidental contamination, for the original case from which Levaditi obtained a transmissible virus was suffering from herpes labialis at the time of death and later 'successful' transmissions were obtained, in a number of instances, from nasopharyngeal washings where the herpes virus is common. In addition, the likelihood of accidental transmission is increased by the fact that Levaditi only obtained one positive result in thirty experiments. Flexner also obtained the virus of herpes from the cerebrospinal fluid of a case of neurosyphilis, showing, therefore, that it may be present in the cerebrospinal fluid in other than cases of epidemic encephalitis.

However, since this date, much further work has been done on the viruses of herpes and epidemic encephalitis, and on their relationship, which goes some way towards answering the above criticisms. Before this is dealt with, some of the work, not generally confirmed, on the nature of the encephalitic virus will be mentioned. Freeman isolated from the brains of fatal cases a small diplostreptococcus in curved chains and accompanied by minute filter-passing bodies and large coccoid bodies. He states that intravenous injection of these organisms into rabbits produces a tendency to localisation of the subsequent infection in the brain. The animals show neurological signs, e.g., paralysis, forced movements, rigidity and inco-ordination. Post-mortem examinations showed an acute or subacute meningoencephalitis with no specific signs of inflammation outside the central nervous system. His virus was transmissible from animal to animal and gave similar findings on intracerebral inoculation into monkeys. Rosenow has prepared an antiserum to this organism from horses and reported good results in treatment of acute cases. This antiserum might be experimented with in any future epidemics of encephalitis and its effects on chronic cases tried. Similar unconfirmed work has been done by Crofton. He stated that in all of eight cases of acute encephalitis the influenza bacillus had been found, and that he had obtained curative results in acute encephalitis by the use of a pure influenza antigen. Other observers have reported good results in treatment by pure influenza antigen (Keith) and also have found the influenza bacillus present in fatal cases, e.g., in the spleen. The relationship between influenza and encephalitis has, of course, been widely discussed and the general view is that they are unrelated. Nevertheless an antigen of Pfeiffer's bacillus can be experimented with and its results, if any, estimated.

On account of the general confirmation that it has received and the large scale on which it has been carried out, the more recent work on the relation of herpes febrilis to epidemic encephalitis is of much interest and importance. The chief advance in this field is due to the work of Perdrau. His findings and conclusions, and also those of other recent workers in this field, will be discussed.

Levaditi, and all observers since, agree on the extreme difficulty of transmitting the virus of encephalitis, even by intracerebral injection of infective brain-pulp from a fatal acute human case, to animals. However, when an apparent transmission has been obtained the virus can be passed in rabbits from animal to animal by appropriate intracerebral inoculation.

Those who considered that they had successfully transmitted the encephalitis virus showed that it was possible to immunise rabbits against it; they compared the encephalitis produced by this virus in rabbits with the encephalitis produced by inoculation of the virus of herpes febrilis; they demonstrated the essential clinical and pathological similarity of the two conditions and the fact that the virus of one immunised the animal against the virus of the other. They concluded that the virus of epidemic encephalitis was closely related to that of herpes febrilis and, also, that the virus of epidemic encephalitis had a greater tendency to localise in the central nervous system and that of herpes to localise in the skin. Their further conclusions on these viruses will be mentioned later. The criticism was that the successful transmissions claimed, few in number, were actually transmissions of the herpes virus itself owing to contamination or previous presence of the latter. Also, the tendency of epidemic encephalitis to localise in the central nervous system of animals and of herpes to localise in the skin was said not to represent differences beyond the variations capable of occurring in different strains of the virus of herpes alone. The importance of Perdrau's work is that it shows the reasons why it was that apparently successful transmissions of the encephalitic virus from infected human brain or cerebrospinal fluid were few and far between. By his methods he obtained a high percentage of successful results, in this way rendering unlikely the possibility of mistaking a transmission of the herpetic virus for one of the encephalitic. Thus he produced in rabbits a typical encephalitis with symptoms from each of the brains of three fatal human cases.

He began by examining his stock rabbits for signs of the spontaneous encephalitis found by McCartney in America, and found in the brains of 250 rabbits, and also in a review of past material, no evidence of this disease in this country. Thus he was able to avoid the ambiguous results that the presence of the parasitic disease would have produced. Perdrau followed the example of McIntosh and kept his infective human brains from two to three weeks in glycerin before inoculating rabbits with them. Such brains, which gave negative results when fresh, produced after such treatment a fulminating encephalitis fatal to the rabbits in four days. Perdrau suggested that immune bodies were present in the human brains, together with the virus, and that

prolonged glycerinisation destroyed the former and not the latter. He suggested this as an explanation of why fresh pulp from brains of human encephalitic patients frequently gave negative results on injection into the brain of an experimental rabbit. He also produced successful transmission of the encephalitic virus by inoculating rabbits intracerebrally with infective material during the negative phase of the development of an immunity. He did this by giving on four successive days, first, two intradermal injections of material, and then two intracerebrally. He found that it took eleven days for immunity to be established following intradermal injection of infective material.

Perdrau succeeded in transmitting a virus of less virulence from a subacute human case and produced in rabbits a subacute encephalitis quite different in symptoms from the usual herpetic encephalitis. If, however, a rabbit was immunised (by intradermal injection) to herpes febrilis and then if it received an intracerebral injection of herpes virus as the immunity was passing off, a subacute herpetic encephalitis resulted which was symptomatically and pathologically identical with the former type. In addition, the brains of the animals that suffered from these two forms of subacute encephalitis both yielded a non-transmissible virus. Perdrau's conclusions are as follows.

In epidemic encephalitis there may be :

- (1) Development of a local cellular immunity which overcomes the infective agent and leads to complete recovery.
- (2) Development of a state of local cellular immunity which partially overcomes the infection, the final issue being a fatal one or a chronic infection.
- (3) Failure of development of any immunity and a quickly fatal result.

Theoretically, the virus in the brains of class (3) above would be readily transmissible, but the majority of the cases were of type (2) and material from them would be either completely non-infective or might produce a subacute encephalitis (as above), from which no further active virus could be obtained. If, however, it were freed from immune bodies by prolonged glycerinization, or if its virulence were otherwise increased (by other methods devised by Perdrau), such material might produce a typical encephalitis transmissible to rabbits. Experiments with herpes show that immunity to a weak virus is transient compared with that to a strong virus. "Thus it seems likely that invasion of the human brain by a comparatively non-virulent virus might produce a spreading low-grade infection, attacking cells of least resistance." Perdrau suggests that certain cell-groups, e.g., the cells of the substantia nigra, are less resistant than others. Thus would be explained the progressive character of cases with slight initial symptoms.

In support of his work, Perdrau suggests that herpetic contamination cannot be urged against all workers (Wimmer also mentioned the unlikelihood of many experienced workers being deceived) and adds that the long-lasting differences in dermatropism and neurotropism of herpetic and epidemic

encephalitic viruses that he possesses makes it possible that the two are related but not identical. He describes a case of herpetic infection of the forefinger which lasted for two or more years, during which time the patient showed, intermittently, signs of mild encephalitis.

Greenfield points out that human immunity to herpes is notoriously slight, being essentially a tissue and not a humoral immunity. This accounts for the outbreak of herpes produced by Levaditi in a patient with acute epidemic encephalitis, in whom he injected intrathecally the virus of herpes. Terssier, Marinesco and others, report that patients who have had an attack of epidemic encephalitis are less immune to herpes than others. This point is of interest in connection with Wimmer's view that immunity is very late in developing in human beings with encephalitis; for example, Levaditi destroyed his virus in vitro with serum from a seventeen months' old case, but found that that from a five months' old case was ineffective.

A suggestion, developed at length by Levaditi, has been made, that there is a whole group of infections that attack only tissues of ectodermal origin, i.e., the skin and central nervous system. He has suggested the following as members of such a group—the "ectodermic neurotropes"—the differences in their symptoms being due to the tissue of predilection, either the central nervous system or the skin: rabies, smallpox, acute poliomyelitis, chickenpox, mumps, foot-and-mouth disease, and the "Bornasche Krankheit" of horses. Poincloux has classified some of these diseases in descending order of neurotropism: poliomyelitis, rabies, epidemic encephalitis, herpes febrilis and vaccinia. The occasional encephalitic complications of varicella and mumps are well recognised.

As a result of further work, Perdrau arrived at the following conclusions:

- (1) Herpes febrilis is caused by a living virus, having a semi-saprophytic existence on the mucous membranes of most persons. It is mildly pathogenic to man and is probably responsible for some cases of herpes zoster, by a local invasion of the central nervous system.
- (2) A different strain of herpes virus, very pathogenic to man, is the causative agent of epidemic encephalitis.

Doerr (1924) has summed up the arguments for and against the relationship of herpes febrilis and epidemic encephalitis.

For relationship:

- (1) Numerous workers have recovered a virus from the cerebro-spinal fluid or brain in cases of epidemic encephalitis, which acts like herpes febrilis virus when inoculated into rabbits. Differences in dermatotropism and neurotropism of the two are not greater than may be observed between different strains of herpes febrilis virus (but see Perdrau's conclusion above).
- (2) Herpes virus may cause lesions and clinical pictures in animals much like those of epidemic encephalitis in man.

- (3) Herpes virus in animal experiments tends to travel from the portal of entry along nerves to the central nervous system.
- (4) Epidemic encephalitis is an infectious disease and no other causative agent has been found.

Against relationship :

- (1) Herpes febrilis is common. Epidemic encephalitis is rare.
- (2) The occurrence of epidemic encephalitis is not accompanied by an increase in incidence or severity of herpes.
- (3) A conclusive example of encephalitis as a sequel of labial or corneal herpes is not known in man (but see case quoted above).
- (4) Encephalitis is not produced in man even by intrathecal injection of herpes virus.
- (5) Herpes is rare in epidemic encephalitis compared with pneumonia or meningococcal meningitis.
- (6) Herpes has been found in only a small number of cases of epidemic encephalitis where it has been specially sought for (two out of 41 cases—Levaditi).

These pros and cons may be judged in the light of the work detailed above. Many critics of this work are convinced that epidemic encephalitis is a 'new disease' altogether. Presumably they postulate a 'new' organism. Is it likely that some 'new' pathogenic organism could suddenly be created? It is more probable that the causative organism of epidemic encephalitis is a variant of some other organism, e.g., of the virus of herpes, or possibly, of some organism previously non-pathogenic.

The workers on the viruses of herpes febrilis and epidemic encephalitis and their relationship regard both as being filter-passing and, otherwise, of an unknown nature. Arguing from analogy with other epidemic diseases of the central nervous system, e.g., acute anterior poliomyelitis and cerebrospinal meningitis, it is very probable that the nasopharynx harbours the organism and that carriers of the latter may exist. Crafts reports a striking example suggesting the infectivity of buccal or pharyngeal secretion. Three soldiers lay in bed, side by side, the one in the middle bed having suffered from epidemic encephalitis. They were in the habit of passing a cigarette from mouth to mouth. The other two soldiers developed the disease. Some cases begin their acute attack with severe gastrointestinal symptoms. Here the alimentary canal may be the portal of entry.

Flexner (1928) continues his criticism of the theory of a relationship between herpes febrilis and epidemic encephalitis; he still considers that it has not been successfully transmitted to experimental animals and that nothing is known of the virus. He has, however, obviously overlooked Perdrau's work, as he still states that there are only six examples of alleged successful transmission of the encephalitic virus to animals reported in the literature.

CONTAGION.

There is an absence of evidence of obvious contagion in this disease. Most of the definite examples show that the contagion occurred during an acute attack, during either the initial or a recrudescence. There is negligible evidence of contagion in the chronic stage. Parsons, from an examination of the records of 1,273 cases, of all types, finds 32 of possible contagion, and Netter from 174 finds eight. Together this gives a percentage of 2.5 (Hall).

CONCLUSION.

In conclusion it may be said that the present position of our knowledge of the virus of epidemic encephalitis is not a hopeless one, and that in the event of more epidemics the results so far obtained afford an excellent starting place for further advance. What knowledge of the virus has so far been gained is useless in affording means of experiment in specific treatment (owing to the transient nature of human immunity to herpes), unless the views of Crofton and Rosenow are taken as a basis. The balance of evidence must be regarded as being conclusive of a persistence of infection in the central nervous system in some cases of Parkinsonism. The only means of detecting this is by observing clinical signs of progress of the disease. The evidence makes it certain that active infection may be present for a considerable length of time before any signs of progress occur. It is, therefore, advisable to treat all cases of epidemic encephalitis, including those of Parkinsonism, for some years at least after onset, as cases of active infection in the central nervous system. This can only be carried out, with the generally unconfirmed exceptions mentioned above, by non-specific means. The durable nature of the Parkinsonian syndrome once it has appeared, and the destructive signs found in the substantia nigra, indicate that the signs and symptoms at any moment must be regarded as being almost wholly due to neuronal destruction and that no remission of them can be expected from non-specific (or specific) treatment of the active infection, even if it were successful. The most to be hoped for is inhibition of the progression.

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