Critical Review.

ENCEPHALITIS AND SPECIFIC FEVERS.

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The term 'encephalitis' signifies in the most general manner an 'inflammation' of brain substance, due to activity of micro-organisms, viruses, or toxins. It is in common usage for a large and heterogeneous variety of conditions, to not all of which can it legitimately be applied. Recent controversies have shown up prominently the uncertainties surrounding the conception of 'inflammation' itself, hence 'encephalitis' is doubly suspect. The old cardinal signs of rubor, calor, tumor, and dolor cannot be regarded as typical of inflammation in the neuraxis; to-day their place is taken, in respect of the nervous system, by parenchymatous (ectodermal) changes and by exudative, infiltrative, and proliferative reactions on the part of the mesoderm (vascular and connective tissues); and these features of histological response to foreign irritants undoubtedly constitute a kind of anatomical definition commanding general acceptance. But perplexities begin as soon as we try to discover the meaning of individual tissue-reactions or draw etiological conclusions from the histological syndrome.

Even if we restrict the expression 'encephalitis' to cases with recognisable mesodermal processes, no specificity attaches to their etiology; on the contrary, disease-conditions that are conspicuously diverse on the clinical side (such as poliomyelitis, epidemic encephalitis, rabies, neurosyphilis, nevertheless resemble each other more or less closely as far as conjunctivo-vascular tissue-response is concerned, though alterations of the neural parenchyma may be less uniform; moreover, one and the same toxi-infection often enough exhibits notable histological variations in different instances (cf. epidemic encephalitis without obvious 'inflammatory' evidence), and, there is reason to believe, at different stages of the same case. With such infections as tetanus, diphtheria, or typhoid fever parenchymatous change is paramount and mesenchymal modifications often negligible, or even absent.

From the standpoint of pathological anatomy it seems possible to distinguish several types of tissue-reaction all of which still pass under the heading 'encephalitis' and emphasise afresh its indeterminate nature.

1. Acute parenchymatous alteration of nerve-cells, toxi-degenerative in character, with hyperæmia and œdema, but with little or no vascular and connective-tissue reactions, and no hæmorrhages. This should correspond in reality to a toxicosis rather than an encephalitis.

2. Acute encephalitis of the genuine histological kind, with cellular infiltrates and exudates ; if with visible hæmorrhages, then 'acute hæmorrhagic encephalitis.'

3. Acute 'encephalitis' of which the prominent if not as yet admittedly distinctive feature is perivascular demyelination, as observed in postvaccinal and some measles cases, and in some types of what is called 'acute disseminated encephalomyelitis.'

Whether these variants represent essential differences or not it is premature to discuss. There is something therefore to be said for the attitude of the clinician, who, accepting the classical symptoms of fever, malaise, headache, clouding of consciousness, and so forth (with or without focal cerebral signs), as indicative of 'inflammation,' includes under the caption of 'encephalitis' all types of case in which the syndrome can be recognised. Unfortunately, however, in some forms it is never pronounced, while it may characterise others not appropriately designated by that name.

In the absence of aid from bacteriological science classification for clinical purposes becomes rather indefinite, and the uncertainty is accentuated by the fluctuating nature of present-day conceptions, as well as by the many still existing lacunæ in neuropathological knowledge. The subjoined scheme embraces types of encephalitis which from a clinical standpoint can be usefully distinguished, despite pathological obscurities.

1. Acute non-suppurative encephalitis.
2. Suppurative encephalitis.
3. Postvaccinal encephalitis.
4. Epidemic encephalitis.
5. Acute polioencephalomyelitis (Heine-Medin disease).
6. Acute hæmorrhagic polioencephalitis (Wernicke).
7. Acute disseminated encephalomyelitis.
8. Encephalitis periaxialis diffusa (Schilder).

Of these groups, perhaps only the fourth and fifth stand for nosological entities ; a variety of toxic or organismal agents is responsible for the first and second, while the nature of the third is still sub judice ; the sixth is probably not as specific as was once thought ; the seventh and eighth offer suggestive links with disseminated sclerosis.

Looking only at the first of the above categories, the clinician is aware that his diagnosis must always be fraught with uncertainty. When in the course of a known toxicosis or infection the patient develops general cerebral symptoms such as headache, fever, malaise, delirium or coma, with or without convulsions, and with or without focal signs such as aphasia, Jacksonian epilepsy, paralysis, and involvement of cranial nerves, the observer believes himself justified in assuming a diffuse or patchy encephalitis to account for them, and doubtless in some instances this is actually the case. But pathological examination has

proved many examples of this syndrome to have been derived not from encephalitis in the strict sense but from vascular states of thrombosis, hæmorrhage or embolism, or from a circumscribed or generalised serous meningitis. At present no means of making a definite pathological diagnosis *intra vitam* is at the clinician's disposal, nor, indeed, is it a simple matter to say histologically where 'encephalitis' ends or begins.

The situation is further complicated by ignorance of the actual viruses of various infections, their nature and classification, and the question whether this one gives rise (usually or constantly) to encephalitic reaction, that to vascular thrombosis or hæmorrhage, another to direct parenchymatous toxicosis, and the next to meningitis serosa.

Whether any so-called 'primary' encephalitis exists (apart from the polioencephalitis of Heine-Medin disease) is debatable. One of the reputed causes of residual infantile cerebral hemiplegia is an acute encephalitis of the Strümpell type (asserted by Gowers to be a "theoretical disease"), separable from both acute polioencephalomyelitis and the alleged encephalitis of the specific fevers. That some type or types of this kind—an encephalitis of unknown origin—do in fact exist must be admitted. But whether these, in their turn, can be distinguished from what is termed, comprehensively, acute meningoencephalomyelitis or acute disseminated encephalomyelitis is far from being settled. From time to time unclassified cases, singly or in small and local epidemics, of an acute nervous affection (in juveniles usually), describable on clinical and perhaps on pathological grounds as acute encephalitis, encephalomyelitis, or meningoencephalomyelitis, have been reported (Brain and Hunter, Gordon, Pette, Redlich, Martin, Brown and Symmers, Anderson). Their separation from some other kinds of encephalitis seems justifiable on the basis of absence of any recognisable specific or predisposing cause. Some of these cases have been described as 'acute disseminated encephalomyelitis' even though the topographical variations are considerable but without signs of dissemination, ranging from the usual picture of acute encephalitis to that of meningismus or meningitis, or of pure spinal myelitis. That they are distinct from the encephalitis variant of ordinary poliomyelitis is determined (e.g., in the Brain and Hunter series) by the simple fact of the spinal fluid being returned as normal (except perhaps for moderate protein increase), without cytological reaction, and by the negative result of animal inoculation experiments.

The 'encephalitis' of the acute fevers, exanthematous or otherwise, next requires examination.

1. MEASLES.—The 'nervous complications' of measles embrace cerebral and spinal symptoms of mild or severe degree, which are encountered in rather less than 4 per 1,000 cases (Boenheim). Beginning during the first week, as a rule, the syndrome is one of headache, mental clouding, meningeal irritation and perhaps convulsions; or of multiple focal invasion referable to cortex,

basal ganglia, cerebellum, and spinal cord; or of single localised lesions in cerebrum, cerebellum, or cord. Toxic psychosis represents another clinical type, while a narcoleptic syndrome in 'cerebral measles' is mentioned by Lust. Acute ascending spinal paralysis is known (Box). Papillœdema has been seen, and a moderate cytological and protein increase in the spinal fluid. Of some 125 cases (12 personal) collected by Ford, complete recovery, noted in all of the first type of syndrome mentioned above, occurred in only 39 of the remaining 116; the usual residua were hemiplegia with or without aphasia, cerebellar defect, and paraplegia. Transient paralyses were observed in a series reported by Aaser.

The pathology of the condition can be summarised as comprising hyperæmia, multiple minute hæmorrhages, and a characteristic demyelination round many of the small veins, with infiltration, in these zones, of lymphocytes or polymorphs; perivascular cuffing otherwise is inconstant; glial cells are often swollen, and the parenchyma suffers secondarily, sometimes severely. Thus the change is partly inflammatory, partly toxi-degenerative; an acute hæmorrhagic encephalitis may predominate (Turnbull, Winnicott and Gibbs, Musser and Hauser), or perivascular demyelination (Wohlwill, Greenfield).

2. SCARLET FEVER.—The occurrence of nervous complications in scarlatina is rare, and pathological examination by modern methods even rarer. Aside from the general syndrome of 'encephalitis,' or of meningitis or menin-gismus, the commonest clinical symptom is hemiplegia with or without aphasia, and next comes a form of neuronitis or of peripheral neuritis. Amaurosis (possibly of uræmic origin) and optic neuritis have been described. Scarlatinal psychoses are not infrequent.

On the pathological side thrombosis, embolism, small hæmorrhages, meningitis, and encephalitis have in turn been reported, but only a very few cases have really undergone the essentials of present-day investigation (Rhein, Southard and Sims, Toomey and Dembo), and in these acute hæmorrhagic encephalitis was the finding. The encephalitis cerebelli of Schilder's case was merely a clinical diagnosis. The accompanying Table, modified from Rolleston, exemplifies the uselessness of guesswork if verification is not forthcoming.

Alleged Causes of Post-scarlatinal Hemiplegia in 73 Cases.

Uræmia	19	Verified p. m. in one case. " " " " " three cases " " " " " " " "
Cerebral embolism ...	14	
Cerebral thrombosis ...	10	
Cerebral hæmorrhage ...	8	
Encephalitis	3	
Cerebral atrophy ...	2	
Cerebral sclerosis ...	2	
Toxæmia	1	
Not stated	14	
	<hr/> 73	

3. WHOOPING-COUGH.—Relatively less uncommon in whooping-cough, nervous symptoms consist of hemiplegia, double hemiplegia, aphasia, bulbar affections, mesencephalic syndromes, and others, with perhaps a special tendency to visual troubles, e.g., optic neuritis.

Their basis, often considered hæmorrhagic (venous or arterial), due to paroxysmal coughing resulting in cerebral congestion, is stated by Neurath to consist rather of hæmorrhagic encephalitis; but according to the most recent studies (Husler and Spatz, Neuburger, Singer, Ford) the cardinal histological change is one of severe degeneration and loss of cortical cells local or diffuse, with moderate glial reaction on the part of astrocytes, oligoglia being in a state of acute swelling. In some places the gyri resemble a mere glial sponge. Mesenchymal alterations in both brain and meninges are minimal and scattered, or absent. The process, indicative of a toxi-degeneration, affects subcortical ganglia and cerebellum to a less extent, and white matter is practically uninjured. It is worth noting that in most of these instances the clinical syndrome was one of convulsions with rigidity. A lymphocytosis (200 per c.mm.) in the spinal fluid, with a small hæmorrhage in the occipital lobe, was nevertheless found by Jochims, and a hæmorrhagic meningoencephalitis by Rhein.

4. MUMPS.—The occasional development of symptoms of a nervous kind in the course of mumps is an old observation, and not, in these days, rare; in 476 cases among soldiers nine were thus complicated (Haden), and it is stated that some 150 are on record. A meningeal reaction in the spinal fluid is found in nearly all such cases (Casparis, Feiling, Chauffard and Boidin, Dopter), but has also been noted frequently in the absence of meningeal or meningismal signs (Monod, de Massary). While the usual history of headache, fever, nausea, vomiting, neck rigidity and Kernig's sign, together with fluid pleocytosis, is suggestive of meningeal invasion, other clinical evidence perhaps points to an encephalitis. Thus among the symptoms observed in cases collected by Acker are unilateral fits, monoplegia, hemiplegia, aphasia, sensory disorders, and those of a toxic psychosis. In not a few instances only cerebral symptoms occur. Optic neuritis occasionally develops. As a rule nervous sequelæ appear as the parotitis is subsiding, but not always (Bedingfield).

Few necropsies have been held; in four fatal cases examined by Gordon (one with a spinal lymphocytosis of 6,800 per c.mm.) the only changes detected were scanty and variable lymphocytic infiltration of the pia and insignificant glial increase; in the medulla of one case slight cellular exudation had taken place. The same observer states he has produced fatal meningoencephalitis in a monkey by inoculation with the filtrate of a gargle from an ordinary case of mumps without nervous manifestations. Up to the present, then, little pathological evidence of actual encephalitis has been forthcoming, and this diagnosis rests almost entirely on clinical deduction; meningitis seems the usual basis for the nervous symptoms (Kaunitz).

5. **TYPHOID FEVER.**—The cerebral and meningeal complications of typhoid have been the subject of many communications since that of Gubler in 1860. According to a recent study of 3,000 cases occurring in epidemic form, neural types appeared in 4.8 per cent. (Garkawi). They may be regarded as general and diffuse, or local. In the former are placed a meningeal or meningocerebral group, with a semiology of headache, pains, motor unrest, tremors, Kernig's sign; and an encephalic group, with deep clouding of consciousness, 'twilight' mental state, amnesia, delirium, stupor, or more pronounced derangement like that of a toxic psychosis, with hallucinations or delusions. Among the latter are such symptoms as aphasia, hemiplegia, athetosis, paralysis of cranial nerves; optic neuritis is a rare occurrence. Mention must also be made of spinal and peripheral types, sometimes like that of a disseminated myelitis, or an acute ascending syndrome, or a limited atrophic palsy as in poliomyelitis.

Where nervous phenomena occur the spinal fluid is commonly but little altered, even in severe cases; no pleocytosis is found, and only a slight increase in protein, up to .05 per cent.; Eberth's bacillus is not seen. But in a minority the fluid is not quite clear; cells increase in quantity, and the bacillus can be cultivated from it. This variety has been described as pure 'meningotyphoid,' without intestinal signs (Cottin and Saloz).

The pathology is variable; it consists of a cerebral toxicosis of parenchyma, without inflammatory reaction (no infiltrates, no bacteria); or of a serous meningeal reaction with increased permeability. The encephalitis mentioned by Raschofsky does not conform in its entirety to our definition. In the case of focal manifestations, however, their usual basis is embolic, thrombotic, or hæmorrhagic (Osler, Williams, Parisot, Hruska, Hawkins, and many more). Transient cerebral symptoms doubtless result from the toxicosis already mentioned, more persistent symptoms from the other types of lesion.

7. **TYPHUS FEVER.**—Symptoms similar to those which may follow typhoid have been met with in the course of typhus fever, the recrudescence of which during the War has been responsible for a number of useful studies. Both central and peripheral disorders are known; of 44 cases in a Polish epidemic hemiplegia with or without aphasia characterised 22, peripheral symptoms 13 (polyneuritis, brachial neuritis, sciatica, peroneal and tibial palsy); two cases of Jacksonian epilepsy occurred, and one suggestive of disseminated encephalomyelitis (Demianowska). Devaux's observations of 215 cases at Passy in Roumania may also be given, in tabular form, as follows:—

110 organic lesions	...	...	...	...	<div style="display: inline-block; vertical-align: middle;"> <div style="font-size: 3em; vertical-align: middle;">{</div> <div style="display: inline-block; vertical-align: middle;"> 59 polyneuritis. 46 hemiplegia. 5 cerebellar syndrome. </div> </div>
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70 functional disorders	...	...	27 difficulty in walking.
			15 functional monoplegia.
			8 deaf-mutism.
			15 functional tremor.
			4 camptocormia.
			1 amaurosis.

28 asthenia, with neuralgia and emotional disturbance.

5 psychic disorder, with mental enfeeblement.

2 existing organic affection, aggravated by typhus.

The spinal fluid sometimes exhibits cloudiness, xanthochromia, heightened coagulability, positive Noguchi reaction, and a mainly lymphocytic pleocytosis (Danielopoulou, Paulian). The infective agent undoubtedly exhibits affinities for the nervous system; from the outset, or very soon after, the clinical picture is more or less typical of meningeal invasion, and equally soon, or in due course, encephalospinal and peripheral complications may develop. Except for benign forms, few indeed, if any, are the cases which do not manifest nervous symptoms.

In rapidly fatal examples of the affection intense hyperæmia of the meninges is found, with hæmorrhagic effusion in these and in the encephalon; foci of softening are sometimes produced in older cases. Histological studies (Wohllwill, Ceelen, Hassin, Wolbach) have shown the main features to consist of proliferative changes in the leptomeninges, diffuse vessel alteration throughout the brain, with endothelial swelling in capillaries and precapillaries, perivascular exudates, small pericapillary hæmorrhages, thrombosis, patchy arteritis, and regressive changes in the intima. In the grey matter, especially of the brain stem from midbrain to medulla, but also of the hemispheres and cerebellum, and to a less extent in the white, are found numbers of so-called 'typhus nodules,' which are invariable if not pathognomonic. They consist of perivascular collections of glial and less definitely of mesenchymal (adventitial, endothelial, polymorphonuclear, rarely lymphocytic or plasma) cells in confused abundance; the central vessel or capillary is usually thrombosed yet may be seemingly normal. The glial elements include microglia and astrocytes. So compact are these nodules that it is possible a syncytial formation occurs. Massing solely of neuroglial tissues may also be seen, taking the shape of glial stars, rosettes, or ray-appearances (Spielmeyer, Nicol). Parenchymatous lesions are confined largely to acute ganglion-cell change of the Nissl type, with dendritic swelling and not infrequent neuronophagia. The rickettsia itself is traceable in the endothelium of cerebral vessels and sometimes in the typhus nodules. Apart from these, perivascular exudates embrace the usual components of lymphocytic, plasma, and compound granular cells.

The peculiar mixture of glial and mesodermal proliferative reactions constituting the nodules has been taken by some for a special variety of encephalitis; but Pollak considers it similar to so-called 'salvarsan encephalitis'

and not to be sharply distinguished from other toxi-infective processes, a view supported by Hassin. By intraperitoneal injection of the Weil-Felix bacillus analogous lesions have been produced in the guineapig brain (Friedberger and Schroder).

8. **VARIOLA.**—Detailed information as regards the nervous complications of smallpox is difficult to obtain, and precise pathological data are extraordinarily meagre. Among the symptoms of 13 cases collected by Glanzmann from the literature mention is made of aphasia, ataxia, hemiplegia, and paraplegia. A Landry type of acute ascending paralysis was a feature in another case (Eichhorst).

The pathological picture in Spiller's case closely resembled that of acute poliomyelitis; in Eichhorst's, that of acute disseminated meningomyelitis. As far as I can discover, none of the pathological investigations is of recent date or modern in technique, and little reliance can be placed on some at least of them. There is at present no justification for assuming the basis of the clinical syndromes to be an encephalitis, and any theory of their origin is largely conjectural.

9. **VARICELLA.**—Not much more is known of nervous chickenpox than of smallpox. Attention, it is true, is being paid to the subject, but less speculation is wanted, and more pathological research.

Chorea, tremor, hemiplegia, cerebellar ataxia, paraplegia, aphasia or dysphasia, optic neuritis, polyneuritic syndrome, meningeal syndrome, and acute ascending paralysis, are among the remarkable clinical diversities attributed to the affection (Wilson and Ford, Waldman, Winnicott and Gibbs, Galli, Krabbe, Chavernac, Wharton Smith, Crouzon and Liège). Commencing some five to fifteen days after onset of the varicella, these nervous phenomena stand in no relationship to its severity. Lymphocytosis and protein increase have been found in the spinal fluid.

No pathological investigations of any value are on record, so far as I have been able to discover. It is clearly improper to assume an encephalitis solely because of the occurrence of cerebral symptoms, aside from the predominance of meningeal, spinal, and neuritic manifestations in perhaps a majority of instances.

10. **DIPHTHERIA.**—Since peripheral lesions undoubtedly characterise most cases of nervous diphtheria it is perhaps not necessary to proceed further with their discussion in this place. Although for the somewhat rare hemiplegia and other cerebral symptoms of the disease an embolic origin is usual, some evidence suggests the possibility of a 'central neuritis' akin to encephalitis.

Any neurologist of critical mind who studies the information here collected from a large number of scattered sources must be impressed with both the clinical and the pathological heterogeneity of the effects on the neuraxis of the diverse noxæ of the specific fevers and exanthems; and he must admit that it is quite illegitimate to assign these effects, one and all, to 'encephalitis.'

This pathological term is getting overweighted, and, as we have seen, is applied in circumstances where it is perhaps not histologically justified. It is no more in reality than a 'pathological syndrome'—it has no more specific etiology than any 'clinical syndrome'; and a study of the pathology of the various fevers proves that in numerous instances 'encephalitis' in a strict sense is conspicuous by its absence.

Further, it may be seen pathologically in conditions which are brought about not by biological but by chemical agencies. According to the English Salvarsan Committee's Report (1922), about 50 per cent. of 'salvarsan deaths' in all countries have been due to a 'hæmorrhagic encephalitis,' characterised histologically by abundant small perivascular hæmorrhages, and by thrombosed capillaries with minute pericapillary necrosis; on occasion hyaline thrombi are found. In other salvarsan deaths, however, only hyperæmia and œdema of the brain have been noted. Multiple minute capillary lesions of this kind are known also in connexion with carbon monoxide and phosgene gas poisoning. And there are many other chemical intoxicants whose action on the nervous system results in the appearances of one or other type of 'encephalitis,' as described at the outset.

The present state of knowledge, therefore, precludes any attempt to correlate encephalitis and specific etiological agents, and compels us to suspend judgment. As far as can be seen, the evidence which some take to suggest that certain types of virus or noxa are associated with certain forms of encephalitic reaction is in reality insufficient. At any rate, the whole subject needs continuing and intensive investigation.

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