term "disseminated encephalo-myelitis of the post-vaccinal type." The question of the relation between acute disseminated encephalo-myelitis of the post-vaccinal type, acute and chronic disseminated sclerosis, and encephalitis periaxialis diffusa is one which others here are more competent to discuss. In the above remarks I have placed in one group the cases of post-vaccinal encephalitis with those which appear to have shown essentially the same histological picture, and have separated this group from acute disseminated sclerosis. Wohlwill (1928) has pointed out the cardinal point of differentiation: the whole length of a vessel is surrounded by demyelination in the former and only a segment in the latter. But the pathogenic processes are essentially similar; consequently the different pictures may simply represent modified reactions to a single agent, and the histological differentiation be artificial. I find it impossible to consider acute and chronic disseminated sclerosis to be other than varieties of one condition; transitions between the two and mixtures of the two have been the rule rather than the exception in my experience.

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ENCEPHALO-MYELITIS IN VIRUS INFECTIONS AND EXANTHEMATA.

AN EXPERIMENTAL AND PATHOLOGICAL STUDY.*

BY

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THAT an encephalitis or an encephalo-myelitis is at times liable to appear during certain acute infections has been known for some considerable time. Our knowledge, however, of the exact nature of this complication in some cases is very scanty. Encephalo-myelitis, whether primary or secondary, may be divided into two main groups—(a) purulent, and (b) non-purulent. The purulent form is the result of the localization of some pyogenic bacterium in the brain substance, while the non-purulent is usually the result of a virus infection, and it is this form which is under discussion to-day. Encephalo-myelitis is found in such virus infections as poliomyelitis, encephalitis lethargica, small-pox, vaccination, chicken-pox, measles, mumps, typhus, etc., and with these I propose to deal in the above order.

POLIOMYELITIS.

Symptoms suggestive of cerebral irritation are not uncommonly met with in cases of acute anterior-poliomyelitis, while in a few instances a definite encephalitis occurs, and to this form the name cerebral poliomyelitis has been applied. True cerebral poliomyelitis, however, is relatively rare, thus Wickmann, in the great Swedish epidemic of

1905, did not see any definite cerebral cases, and none were recorded by Peabody, Draper, and Dochez in the great New York epidemic of 1909. The first cases were described by Strumpell in 1884, and to them he gave the name poli-encephalitis, but in the light of our present knowledge it seems very probable that many of his twenty-four cases were not cases of true poli-encephalitis. It is certainly true that in the majority of the fatal cases of poliomyelitis small focal areas of encephalitis can usually be demonstrated in the cortex to the brain, while in the experimental disease in monkeys, although the major lesion is always in the cord, focal areas of inflammation can be found in the brain.

My own investigations have convinced me that an extensive cerebral involvement in acute anterior poliomyelitis is unusual and, as a rule, the lesions in the brain are slight and mainly consist of a few scattered areas of perivascular cellular infiltration of vessel sheaths.

Experimental Disease.

An experimental infection can readily be produced in monkeys by the inoculation of infective material from cases of poliomyelitis. The animal develops, after an incubation period of about a week, a very definite flaccid paralysis, and histological lesions in the cord identical with those in human cases are found. The maximal lesion is always found in the cord, no matter how the infection is made. In most cases isolated lesions are also to be found in the brain, and particularly in the grey matter at the base. Rabbits can also be infected, but with some difficulty.

ENCEPHALITIS LETHARGICA.

In encephalitis lethargica the main pathological lesion is an encephalitis of varying intensity, but, as a rule, most marked in the basal ganglia of the brain, while the cord is generally unaffected. The most characteristic histological lesion is a well-marked perivascular sheath infiltration, forming at times quite a distinct cuff round the vessel. The infiltration consists chiefly of lymphocytes with a number of plasma cells. Polynuclear leucocytes are conspicuously absent. In addition, there is a certain amount of infiltration of the perivascular parenchyma and glial proliferation. The nerve cells are usually not affected.

Experimental Disease.

As is generally admitted, encephalitis lethargica appears to have been unknown till the outbreak recorded by von Economo in 1916 in Vienna. I had the opportunity of examining some of the earliest cases which occurred in this country, and early came to the conclusion that we had to deal with an entirely new lesion and disease. In collaboration with Professor Turnbull, I was successful in inoculating material from an acute outbreak into monkeys and rabbits, and reproducing symptoms and lesions which showed great similarity to the natural infection in man.

Some writers have confirmed our findings while others have failed to do so, and base their arguments mainly on two grounds: (1) failure to produce any lesion at all, and (2) that lesions found in the experimental rabbit are due to the spontaneous encephalitis of rabbit, and not to the inoculum. But the great similarity of the lesion in man to that of the experimental disease in rabbits may be seen in photomicrographs, while histologically the spontaneous encephalitis of rabbits is quite another type, and no one familiar with the two lesions could use the second argument.

SMALL-POX.

Clinical accounts of small-pox contain frequent references to the appearance of symptoms which suggest involvement of the nervous system. For instance, there may be convulsions and delirium during the first fever or during the eruptive stage, while later there may appear definite parietic manifestations. A full account of the literature dealing with nervous complications of variola has been given in an earlier paper by Professor Turnbull and myself, so it is unnecessary to give it in detail here.

Fortunately, owing to the kindness of Dr. Garrow, medical officer for Chesterfield, I was able to examine the brain of a child who developed cerebral symptoms after

* Read in a discussion in the Section of Pathology and Bacteriology of the Annual Meeting of the British Medical Association, Cardiff, 1928.

an attack of mild small-pox. Histologically, a very definite type of encephalitis was found.

The histological lesion consists of a perivascular, small-celled infiltration, characterized by a slight infiltration of the vessel sheath, and a more diffuse wide infiltration of the surrounding parenchyma, which often shows well-marked demyelination of the nerve fibres. The cellular infiltration is composed mainly of large cells with oval clear nuclei, together with a number of lymphocytes. Polynuclears are uncommon, as also are plasma cells. The meninges are only slightly involved.

The general appearance of this inflammatory lesion is very striking, and the sharply demarcated vessel, with the surrounding cellular infiltration arranged in an irradiating manner, is strongly suggestive of a tissue culture.

In this case the encephalitis was apparently diffuse in the upper brain, but gradually lessened as one passed down, till in the medulla there was no sign of it. Unfortunately the cord was not obtained for examination. The striking similarity of the lesion to that of post-vaccinal encephalitis will be referred to again.

POST-VACCINAL ENCEPHALITIS.

In recent years a new type of encephalitis has been observed in relation to vaccination, the main clinical and pathological features of which Professor Turnbull has just given you. The occurrence of this particular type of case was noted by him as long ago as 1912, when we were investigating an epidemic of poliomyelitis. In 1926, Professor Turnbull and I published a paper recording our investigations on six cases of this particular post-vaccinal encephalitis. Altogether now some hundreds of similar cases have been published in Europe by Bastiaanse, Lucksch, and others.

As the condition has been fully described by Professor Turnbull I shall content myself with indicating the features which I think have an essential bearing on the etiology of the condition. It is now generally admitted that post-vaccinal encephalitis bears a very constant relation to vaccination, both as regards time and place. The condition manifests itself on the average 10 to 14 days after vaccination as headache, delirium, paresis, and, ultimately, coma and death in the fatal cases.

There has been considerable division of opinion as regards the true nature of this encephalitis; among these opinions two are worthy of mention:

1. That the disease is vaccinal in origin.
2. That the condition is due to the presence of a dormant virus stimulated into activity by the vaccination.

It has been suggested that the dormant virus might be poliomyelitis, encephalitis lethargica, herpes febrilis, or some unknown virus. Neither time nor space allows of a complete analysis of the various views, so I propose to give only those data which I think have a direct bearing on the problem.

Histological Data.

An examination of the lesions of the central nervous system shows that they present a very constant and characteristic histological picture, the main features of which might be summarized much as follows:

1. Wide distribution of lesions in grey and white matter of the brain and cord.
2. Perivascular nature of the lesion.
3. Slight vessel sheath infiltration, with considerable extra-vascular parenchymatous infiltration.
4. Infiltration composed mainly of large endothelial type of cells and glial cells.
5. Perivascular areas of softening or demyelination. Here, as in post-variolar encephalitis, the general appearance of the perivascular cellular infiltration is suggestive of a tissue culture growth.
6. Occasional presence of small focal lesions in the internal organs.

The above lesions, I think, are sufficient to show that we have a new pathological entity, in that the lesions are distinct from those met with in the known virus

infections of the central nervous system—poliomyelitis and encephalitis lethargica. But in order completely to incriminate the virus of vaccinia it is essential that lesions of a closely similar nature can be produced by animal inoculation.

Experimental Data.

Material from the central nervous system of these cases of post-vaccinal encephalitis was inoculated (a) intracerebrally and (b) intracutaneously into rabbits and monkeys. The intracerebral inoculations only produced a slight rise of temperature and some transient paresis; but by special intradermic inoculations into rabbits it was possible to recover vaccinal virus on several occasions. The negative nature of the intracerebral inoculations, to my mind, clearly demonstrates that neither the virus of encephalitis lethargica nor that of poliomyelitis is present, and I think that that of herpes febrilis might be included also, as it has a distinctive lesion and so readily affects rabbits.

The actual presence of the vaccinia virus is not absolute proof, however, that the condition is solely due to the vaccinia virus, as under normal conditions vaccinia virus can be demonstrated in the blood for some days after the vaccination has reached its height. The real proof would be the production of a similar lesion by the inoculation of vaccinia virus, thus conforming to the so-called postulates of Koch.

What, then, is the effect of intracerebral and intravenous inoculations of vaccinia? It has been known for some years that intracerebral inoculations of vaccinia virus into rabbits produces a fatal encephalitis of varying severity, and that there is considerable difficulty in carrying on the inoculations in series (Marie). Levaditi, however, a few years ago, succeeded in raising the virulence of a strain of vaccinia to such a degree that it could be successfully carried on from one animal to another. To this strain he gave the name of neuro-vaccine. The lesions produced in the brain are more meningeal than encephalitic, and frequently show large areas of necrosis in addition.

My own experiments confirmed the above, in that at first I found it easy to produce an encephalitis with ordinary strains of vaccine lymph, but quite impossible to make passages in series. After many attempts, however, I succeeded in raising the virulence for rabbits of a freshly isolated various strain of vaccine lymph by rapid passage on the skin of the rabbit. This vaccine lymph was of such a virulence that frequently a general eruption, with internal focal lesions, followed in the rabbit after simple cutaneous inoculation.

With the same virus I made a series of intracerebral inoculations, and then found that by this procedure I had got a very highly neurotropic strain for the rabbit. Intracerebral inoculations regularly produced a fatal issue in four to five days, and on examination of the brain very characteristic histological changes were observed. In contrast to what I found before, there were very definite areas of encephalitis in the brain, extensive meningeal lesions, and, at times, definite indications of perivascular softening. In addition, the cytology of these lesions was of the type characteristic of post-vaccinal infiltrations.

These results at once invalidate Levaditi's failure to produce comparable lesions in rabbit's brains with his neuro-vaccine, a negative result which he used as an argument against the variolar nature of the post-vaccinal encephalitis.

Further, I found that intravenous inoculations of Levaditi's neuro-vaccine and of my own high virulent vaccine lymph produced focal lesions in the internal organs of the rabbits. The lesions are, to my mind, absolutely typical of the lesions I found in the organs of cases of post-vaccinal encephalitis, and, to judge from the written descriptions, are similar to the focal lesion that occurs in true small-pox.

The focal lesions were described many years ago as occurring in the internal organs of fatal cases of small-pox, but the histological descriptions are poor and somewhat difficult to visualize. So far as can be gathered there is no modern histological investigation recorded. For some

reason or another it is impossible to obtain pathological material from fatal cases of small-pox. The focal lesions in small-pox are described by Weigert, Chiari, Roger, and Weil; the focal areas can be seen with the naked eye as pale areas about the size of a pea, non-purulent, with central necrosis.

The focal areas observed in cases of post-vaccinal encephalitis are visible to the naked eye, whitish in colour, and somewhat larger than, or about the size of, miliary tubercles. Their general and histological appearance is at first sight suggestive of a tubercle. They differ in that they show more evidence of healing (fibrosis) than is usually found in tubercles; giant cells are prominent features, with a surrounding zone of fibrosis and lymphocytes. The fact that no tubercle bacilli could be demonstrated in the lesions, and the evidence of healing, strongly support the view that they are not tubercles, but granulomata resulting from multiple foci of some virus.

The following summary, based on the above experiments, suggests, I think, that vaccine virus is the causal agent.

1. Intracerebral inoculations of neurotropic strains of variolous lymph produce an encephalitis in rabbits, presenting the main histological characters of post-vaccinal encephalitis.

2. Intravenous injections of neurotropic strains of vaccinia produce focal lesions in the internal organs similar to those found at times in cases of post-vaccinal encephalitis and in variola.

3. The failure to produce any of the known virus infections of the central nervous system by animal inoculation with the material from post-vaccinal encephalitis.

4. The occurrence of a very similar cerebral lesion in a case of encephalitis following on small-pox.

CHICKEN-POX, MEASLES, MUMPS, AND TYPHUS.

Encephalitis, as I have previously pointed out, has been recorded in cases of chicken-pox, measles, and mumps, but such a complication is rare.

In the case of chicken-pox (varicella), clinical records show that symptoms suggestive of an involvement of the central nervous system occur from time to time, and in the literature some dozen cases of encephalo-myelitis have been recorded. An excellent summary of these is given in a recent publication by Wilson and Ford, who record three cases which came under their own care. Recovery in most instances was complete in a few weeks' time. Fatal cases of chicken-pox are rare, so that no histological details are available; so far, I have only had the opportunity of examining the organs from one case of small-pox and, unfortunately, in that case the brain was not available.

Nervous involvement in measles and mumps is still more rare. Recently Wohlwill has recorded two cases of encephalitis during measles, and the histological changes are believed to show considerable resemblance to those found in post-vaccinal encephalitis. But I must reserve my judgement until I have had a chance of examining his work in detail.

Encephalitis in typhus fever is a constant feature, and may, therefore, be regarded as part of the actual disease process. Microscopical examination shows the constant presence of lesions in the central nervous system and internal organs. In general, the encephalitic lesions show a great similarity to those of post-vaccinal and post-variolar encephalitis. The pathological changes have been described by Coelen, Nicol, Spielmeyer, Walach, Todd, and Palfrey, and consist essentially of proliferations of large clear cells into the surrounding nerve tissue with infiltration of inflammatory cells (plasma cells, lymphocytes, and a few polynuclear leucocytes).

Four types of lesions are described, but the two most characteristic are the "compact" (tubercle-like) nodules of cells, and the "rosette" or diffuse perivascular outgrowth. The proliferated cells are generally considered to be glial in origin, but Wolbach and his co-workers are of the opinion that they are mesoblastic and derived mainly from the blood vessels.

As a rule, gross lesions are not visible to the eye, and the meninges show only a slight inflammatory infiltration.

Experimental Disease.

Typhus has been experimentally transmitted to monkeys (*cercopithecus*) by intraperitoneal injections of blood from cases of the disease, and to guinea-pigs by injection of pathological tissue and lice from human cases. The virus can be carried on from guinea-pig to guinea-pig indefinitely by injection. Lesions are found in the central nervous system of these animals identical with those found in man.

SUMMARY.

A non-suppurative encephalo-myelitis can occur in a number of virus infections—in particular, poliomyelitis, encephalitis lethargica, small-pox, vaccinia, chicken-pox, measles, mumps, and typhus fever.

In the case of poliomyelitis, localized areas of encephalitis are not infrequently found in fatal cases and, histologically, the lesions are typical of that known to occur in poliomyelitis.

In encephalitis lethargica the encephalitis is constant and a normal feature of the infection, with characteristic histological lesions.

The encephalitic complication is exceedingly rare in chicken-pox, measles, and mumps, and we know very little about the lesions produced.

In vaccinia and small-pox a very characteristic and diffuse encephalo-myelitis is found. Histological and experimental research have shown that the lesions in the two conditions are identical, characteristic, and definitely distinct from those of poliomyelitis and encephalitis lethargica.

The only virus that could be demonstrated in post-vaccinal encephalitis was vaccinia. Certain strains of vaccinia virus will produce in rabbits a vaccinal encephalitis showing the same type of lesion. These facts lead strongly to the belief that the lesions of post-vaccinal encephalitis are characteristic of the action of the virus of vaccinia on the central nervous system.

An encephalo-myelitis is apparently present in all cases of typhus fever, and here again the histological picture is distinctive, although there are resemblances to those met with in post-vaccinal encephalitis.

GENERAL CONCLUSIONS.

We have seen, therefore, that encephalo-myelitis may occur during the course of several virus infections, either as part of the disease process or as a complication, and investigations of these conditions show that a histological picture of a certain type can be assigned to each. Doubtless further studies will bring forward additional new types as the differential features are better understood. This is well instanced in the case of encephalitis lethargica and post-vaccinal encephalitis, each of which have been ascribed by certain writers to causes other than its specific virus.

The characteristic histological appearances of these conditions, together with the fact that lesions comparable with those found in the natural disease can be reproduced experimentally in animals by the inoculation of virus-containing material, is strong evidence that the encephalitis is actually produced by the infecting virus in each of the above-mentioned diseases.

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