POST-VACCINAL ENcephalitis: Its association with VACCINATION and with POST-INFECTIONOUS and ACUTE disseminated ENcephalitis.

By Prof. Ricardo Jorge, PResident of the Public Health Council of Portugal.

(Concluded from p. 219.)

The virus of our hypothesis is one which only changes its character of inertia and harmlessness under stimulus by the vaccine virus; apart from this contact there is no evidence of its mysterious existence. Might it not at least be possible to catch a glimpse of some other forms of its activity apart from vaccination? Its existence would then come out of the region of theory and begin to be apparent.

Cerebral complications of such infectious diseases as eruptive fevers, small-pox, measles, and chicken-pox have been long known to classical medicine. Vaccinia, forming part of this exanthematic group, it was natural to think of forms of encephalitis together. Under the impetus of the questions raised by the nervous sequelae of the Jennerian inoculation, these cases were no longer looked at as mere clinical incidents, but as documents through which a problem of comparative pathology could be elucidated. It is in England that the greatest progress has been made with the endeavour to bring these forms of encephalitis together. Dr. J. Hutchinson, secretary of the Rolleston Committee, has tabulated the cases brought to his knowledge and has kindly placed at our disposal, together with other useful information, the accompanying Table of fatal cases notified since 1927. Moreover, earlier literature dating back long before the advent of post-vaccinal encephalitis has already also produced some important contributions.

Are these so-called post-infectious types of encephalitis the same as the post-vaccinal? To affirm it on the grounds of clinical similarity alone would be dangerous; the basis of their identification is anamnestic and pathological. Histological examination has shown the identity of lesions in the nervous tissues affected; they present the same Perdrau-scheme. Hence the pathognomonic test, and in face of it the only cases which one ought to consider as definitely proved are the recent ones which have been submitted to the test of the microscope.

Encephalitis Post Infectionem.

MEASLES.

Measles, the commonest of the group of exanthematic diseases, has produced the largest number of examples. The first known case goes back to 1790 (Lucas, cited by Greenfield 24). Fresh cases are collected day by day, but it is difficult to decide if encephalitis after measles is in fact becoming more common or whether practitioners are only now becoming more alive to its presence. One may surmise, however, that they are really becoming more common. Ford 25 was able to recover in 1928 113 cases from the literature to which he himself added 12. There were 25 fatal cases in England for the period 1927–30 inclusive, composed in age-groups as follows:—

<table>
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<tr>
<th>Age-groups</th>
<th>Total</th>
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<tr>
<td>0–5 years</td>
<td>16</td>
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<td>6–15</td>
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Greenfield, 1929, published four observations, the most interesting of which have been included in the Further Report. Benn 28 has lately added two fatal cases with autopsies.

In Germany, Last 31 described in 1928 4 cases, Bergenerfeld 1, Slicht 4, Redlich 1, Wohlwill 32, 2 in 1928 with post-mortem examination. In Austria two were observed by Bregman and Poneck. In France, where Comby had observed two cases in 1924, a case in a normal convalescent after measles has recently been demonstrated by Lechelle, Bertrand, and Fauvert before the Société Médicale des Hôpitaux. At the autopsy it was noticed that the demyelinisation was clearly present, though less accentuated than in others described. In Italy, in 1929, a case was recorded by A. Signa and two by Suvinian (cited by Comby 34). In the United States, Musser and Hauzer 33 recorded eight cases in 1928, collected during the course of an epidemic of 251 cases admitted to the New Orleans Hospital; in 1930, Zimmermann and Yannet gave an account of two cases, and in the following year Ferraro and Scheffer six cases. At Rio de Janeiro, Martinho recorded in 1929 a case of post-measles encephalitis attended by himself (cited by Comby 34). At Montevideo, Morquio 37 published eight personal observations with one death. The types were varied, acute diffuse encephalitis predominating.

This encephalitis occurring after measles presents the following pathological characteristics:

It appears in children, measles being predominantly an infantile disease.

The attack occurs at varying periods after the onset of the measles. It may begin at the very onset of the measles attack. As a general rule, it follows the appearance of the rash at variable intervals—more usually, however, it appears after the defervescence and the rash has disappeared. It has been observed also during convalescence, or several days, or even weeks, after recovery.

Its incidence is not in conformity with the severity of the attack; light attacks can be accompanied or followed by nervous complications. According to Ford, the encephalitis supervenes in four cases out of 1000.

Its fatality is relatively low. Only about 10 per cent. of the cases at the most are fatal; recovery is the rule, although often accompanied by sequelae.

The symptomatology reproduces the forms and the known types of acute encephalitis; the lesonal type conforms to Perdrau's scheme. Proof of this has been plainly demonstrated in recent cases submitted to autopsy and controlled microscopically. For example, the cases of Wohlwill; Greenfield's case, the account of which is given at length in the Further Report; and those of Zimmermann and Yannet, of Ferraro and Scheffer, of Benn, and of Lechelle. Each of these has recorded in much the same language, besides the congestion and the
haemorrhage, a perivascular infiltration, though often very slight, and a typical demyelination.

SMALL-POX.

The series of encephalitis cases following small-pox which have been recently recorded are few in number. Nevertheless, knowledge of nervous sequelae of small-pox extends back for two centuries. Reference is made to them, according to Greenfield, in the writings of Clifton (1724) and Freind (1730) and they have also been observed as following variola inoculation (Dunsdale, 1757) (communication by Dr. Hutchinson). The small-pox inoculation could cause cerebral infections in the same way as cow-pox; nevertheless, even at this distant epoch, if encephalitis complications had been prevalent epidemically among small-pox patients as is the case to-day among vaccinated persons, the circumstances should have been known and recorded. More recent writers recall this occurrence of nervous complication; and among them MacCombie (1905) states that in small-pox the nervous system is more often involved than in the case in other eruptive fevers (cited by Troup and Hurst 33). Rolleston only found 25 examples out of 10,000 small-pox cases in London in the epidemic of 1901-02.

During the five years 1925-29, 23 cases of death from small-pox accompanied by various nervous complications have been registered in England, and some of these were definitely diagnosed as encephalitis. In two of them the encephalitis was duly confirmed; MacCombie described a case of encephalitis following small-pox in 1928, and another, in a man of 63 years, was given by Troup and Hurst. A third case is noted in the Further Report. In all these there was similarity in the clinical facies and identity in the histological findings—a cellular infiltration around the vessels and zones of disappearance of the myelin sheath. A curious case was cited in the Further Report. A boy of nine previously followed up small-pox; two days after the rash cerebral symptoms appeared but he eventually recovered. It is not clear whether the encephalitis should here be put to the account of vaccinia or variola.

The Ministry of Health has unpublished notes concerning four cases, one of which is interesting, not only because of the age of the patient, 63 years, but because of the precocity of the nervous symptoms which preceded the small-pox eruption by two days. It should be noted that encephalitis can occur in variola minor as well as in variola major; as in the case of measles, it does not depend on the severity of the disease. Nervous complications in the case mentioned in the Further Report arose four days after the onset of small-pox; in the Troup and Hurst case the period was 12 days. In that particular case small-pox ran a normal course in 15 other persons who had been infected from the same source.

VARICELLA.

Encephalitis after varicella has been described by various observers, though cases are not common. In 1924-25 Toni and Galli drew attention to this complication of varicella. D. Winnicott and Wills (1926) and Glanzmann (1927) brought forward some new cases, and the latter considered their pathogenesis. Wilson and Ford 48 in 1927 recorded three histories all ending in complete recovery. Jeanne Martin in 1929, Robert Rendu in 1930, and P. Gauchier in 1931, recorded similar cases (cited by Comby 41).

Rake 41 described a very clear case in connexion with which he makes a survey of known literature. Tramer 42 also records a case with encephalitic symptoms. Eight cases have been recorded by the English Ministry of Health, all in infants below 5 years of age. Bouman has recently mentioned a case after varicella which he considered quite characteristic, followed by recovery in a child of 4 years of age who had never been vaccinated (communication of Dr. Jitta). Babonneix 43 attributes to encephalitis the convulsive attacks of Jacksonian type which occurred in two infants with varicella. He also mentions another case, also after varicella, with complication of symptoms. The period of incubation is said to vary from five days from the appearance of the rash to 15 days and even more. The prognosis is quite favourable. There have been no autopsies, so that the diagnosis of typical encephalitis can only be assumed.

MUMPS.

It has long been known that epidemic parotitis can be accompanied by meningo-encephalitis phenomena. Acker, in 1913, was able to collect 30 fatal cases, and several came to light during the war. Bedington (1927) 44 described a case, and refers to previous literature on the subject. R. Holtsch has (1931) given an account of another case with meningeal symptoms occurring two days after the swelling of the right parotid, and has collected 16 fatal cases since 1916. A benign form would appear to be usual in children; the condition seems to be more severe among adults.

The cerebral manifestations occur after the swelling of the parotid, though it seems that sometimes they may precede the appearance of the parotitis. No deaths and no autopsies.

GERMAN MEASLES.

Pierret and Le Marc'Hadour 45 in July, 1931, described to the Societe de Medecine du Nord a case of meningo-encephalitis occurring during mild measles with death after 6 weeks. The first case had been described by Brock 46 in 1929. Debré, Turquety, and Broca 47 also dealt with this type of encephalitis in 1930 on the basis of two observations. In both, though the affection was well-marked, recovery was rapid. Babonneix 43 described a case following rubella accompanied by diffuse lesions in the nervous system and terminating fatally after a protracted development.

No autopsies have been recorded which would determine the precise nature of the affection.

INFLUENZA.

In influenza we have a virus endowed with a selective affinity for the nerve centres. Post-influenzal encephalitis occurs fairly frequently during the course of the great pandemics of influenza, and also during the ordinary seasonal recrudescence. So well was this realised at the time that encephalitis lethargica made its appearance, it was considered natural to regard it as dependent on the universal influenza epidemic of 1918. The British statistics record 90 fatal cases during the period 1927-30, the great majority being adults.

Much has been written on post-influenzal encephalomyelitis and its lesions, but what interests us for the moment is to know whether from recent autopsies it has been possible to discover histological lesions similar to those of post-vaccinal encephalitis. Two cases in adults, studied by Greenfield, were published in the Further Report; one was fatal five days, and the other seven weeks, after the appearance of the encephalitis. The post-mortem examination revealed the same lesions previously seen in encephalitis following other infections—cellular infiltration round the vessels with concomitant demyelination. McAlpine was of opinion that the second case was one of idiopathic encephalitis rather than due to influenza. One might perhaps be more probable that a light and simple infection, such as an angina, a cold, or bronchitis, can originate the encephalomyelitis, whether influenzal or not (G. Buchanan, Report of the Small-pox Committee, 1930). 48
OTHER INFECTIONS.

One cannot pass without remark the occurrence of neuro-paralysis in persons who have undergone the Pasteur treatment after being bitten. These disorders of the nervous centre, recognised since the beginning of the nineties, are rare and do not appear to be attributable to the rabies vaccine. The lesions appear to be quite similar to those of post-vaccinal encephalitis, as Basson and Grinker, among others, have shown in a fatal encephalopathic rabio-vaccinal case.

Mention has also been made of cerebral complications following scarlarina, whooping-cough, diphtheria, &c.

Acute Disseminated Encephalitis.

The title and description of this condition date from the work of Westphal (1872). Further interest in it has recently been stimulated by the view that all the post-infectious types of encephalitis should be classed according to their clinical and anatomical characteristics as special types of disseminated encephalitis. Acute disseminated encephalitis has recently occurred rather in an epidemic fashion, though it has seemed to arise spontaneously and not by any known infectious contact. Consequently there is a special interest in considering these cases in relation to theories of post-vaccinal encephalitis.

Redlich, in 1927, published 13 cases, discovered over a period of three years. These attacked were for the most part adults, over 30 years of age, and were attacked during the winter months. All of them were restored to good health. In the same year, Pette reported 25 similar cases occurring at Breslau and Amsterdam. Flatau records 17 observed cases collected at Warsaw and in other towns during the first half of 1928—an epidemic series of cases with similar symptoms and certain peculiarities. Children and young persons were most frequently attacked. The progress of the disease was benign, and there were only two deaths. The clinical characteristics enabled the condition to be identified with disseminated encephalitis.

Histological examination in the only autopsy confirmed the clinical diagnosis. Analogous cases of acute disseminated encephalitis have been published by Brain and Hunter (1929), Martin (1928), Spiller (1929), Strauss and Rabiner (1930). McGillpine has recently given a detailed clinical picture and account of the lesions in acute disseminated encephalitis, taking earlier work and deductions into account. He adds a set of four occurrences of sequelae which have been established for disseminated encephalitis.

McAlpine, in his detailed monograph on acute encephalitis, in spite of their similarities, depend on different viruses. On the other hand, Courmand, in his detailed monograph on acute encephalitis, regards their identity as proved by the similarities of the histological lesions with those which have been established for disseminated encephalitis, whether post infectionem or spontaneous. Two personal observations, with sections and reference to Pette's cases, supported this identification of multiple sclerosis and disseminated encephalitis.

Conclusions of Part II.

Practically all the authors cited accept, more or less, the doctrine of unity; that one type of virus causes either disseminated encephalitis, whether it is deuterotropic (post-vaccinal or post-infectious) or protopathic (spontaneous). This virus, which has not yet been possible to isolate or handle, must in essence be characterised by its elective affinity for the myelin sheath which undergoes disintegration (demyelinisation). It acts by itself in spontaneous encephalitis, whereas in those following infections it comes into action in the wake of another virus—vaccinia, measles, variola, vaccinia, &c., which open the way for it, or enable it to pass from a latent condition to one of infectious activity.

One can no longer refuse the admissibility of this hypothesis, since it is supported by a dossier of well-established facts and nearly all writers entertain it. Some of them consider the hypotheses of identity as highly probable and others like Pette, Peddrau, Courmand) definitely assert it. The facts brought to support the theory are very striking, although it must be admitted that there are also some discords to consider. The following may be mentioned:

1. While post-vaccinal encephalitis is of recent date, forms of encephalitis post infectionem have long been known, some of them for over a century. The same applies to acute disseminated encephalitis.

2. The frequency of post-vaccinal encephalitis is much greater, in the countries affected, than that of post-infectious or disseminated encephalitis. It seems, however, that cases of the latter may be on the increase.

3. No concomitance in time and place among these different forms of encephalitis has been observed; the post-vaccinal series are not accompanied by cases of disseminated encephalitis, nor vice versa. In Dutch centres, for example, encephalitis was only found among those who had been vaccinated, and not at all among those not associated with this vaccination.

4. A relatively constant period of incubation, which is shown in the post-vaccinal cases, is not evident in post-infectious encephalitis. It may be, however, that we have not yet sufficient numerical data on this matter.

5. The fatality is much higher in post-vaccinal encephalitis than in the others. Disseminated encephalitis is, indeed, conspicuous by its benignity.

6. Post-infectious and disseminated forms of encephalitis are often followed by sequelae, whilst in the post-vaccinal there are very much rarer.

7. The anatomical similarity is not in all respects complete. In addition to the perivascular infiltration and the demyelinisation, one meets with different somatic lesions, such as signs of intense inflammation and hemorrhages, in the case of the post-vaccinal encephalitis.

8. It may be that some of these differences will be effaced as observations continue and increase. The materials are scanty owing to the relative rarity of all these kinds of encephalitis; cases still go undetected, and very few are observed throughout the course and complications of the disease.

Direct proof of the existence of a single virus for all these forms of encephalitis—one which would remove all doubts—has still to be furnished and may be long in coming. The conception of unity rests on another principle be urged that the same histological process is engendered by diverse infections, by diseases which are very different in respect of their aetiology. The pathological proof in itself is hardly sufficient to carry full conviction. But if in place of unity one assumes plurality of the viruses—that is to say, that each encephalitis, post-vaccinal, morbillar, varicular, varies in its own virus which, as the result of its neurotropism, has succeeded in attacking the nervous centres—one then has to ask if it is reasonable to suppose that so many different viruses would attack the nerve tissues in the same manner, with the same destruction of the myelin sheath, and the same microscopic characteristics.

The assumption of a single encephalitogenic virus which is associated with the different viruses of these diseases, followed by the same complications seems to us to be in more logical accord with the facts known up to now. It is, however, simply a provisional synthesis resting at the mercy of scientific progress, which, with the same determination and the same sureness, will remove all doubts.
by pursuing them. It is greatly to be hoped that they will be pursued; that, on the one hand, the investigators will persevere in the study of experimental encephalitis and, on the other hand, that the conclusions and dispositions of encephalitis will be closely followed. All these studies should be vigilant watched. They already come under official supervision in England, Holland, Germany, Sweden, and elsewhere. Medical practitioners should notify any cases recorded by them in order to obtain an examination by an expert neurologist, laboratory determinations, and, in fatal cases, a post-mortem examination by the pathologist of the Ministry of Health in England, who has recently addressed to practitioners a request that they will communicate without delay all cases with acute infection of the central nervous system which have occurred within four weeks after vaccination, or in which the symptoms have immediately followed an acute infectious disease. All such collections of carefully made observations will bring us nearer to wider and exacter knowledge.

REFERENCES.
45. Pierret, and Le Marc'Hadour: Presse Méd., August 26th, 1929.
49. Westphal: Quoted by Flexner, loc. cit. (ref. 23).

PROBLEMS OF WATER POLLUTION.
Four years ago the Water Pollution Research Board of the Department of Scientific and Industrial Research began to issue a monthly series of abstracts on sewage, water-supply, and pollution. In the Board's latest report Sir Robert Robertson remarks that these are stimulating industrial concerns and that individual experiments and researches on pollution should, if possible, be pursued; that, on the one hand, the investigators will persevere in the study of experimental encephalitis and, on the other hand, that the conclusions and dispositions of encephalitis will be closely followed. All these studies should be vigilant watched. They already come under official supervision in England, Holland, Germany, Sweden, and elsewhere. Medical practitioners should notify any cases recorded by them in order to obtain an examination by an expert neurologist, laboratory determinations, and, in fatal cases, a post-mortem examination by the pathologist of the Ministry of Health in England, who has recently addressed to practitioners a request that they will communicate without delay all cases with acute infection of the central nervous system which have occurred within four weeks after vaccination, or in which the symptoms have immediately followed an acute infectious disease. All such collections of carefully made observations will bring us nearer to wider and exacter knowledge.

ULRICH ELLENBOG.
Reference was made in THE LANCET (1931, ii., 809 and 997) to a fifteenth century treatise on industrial hygiene mentioned by Dr. L. Carozzi in his historical review of occupational diseases. It may be of interest to note that this was reprinted in facsimile in 1927 from the only known copy of the first issue in Munich University Library. A copy of this reprint is in the library of the London School of Hygiene and Tropical Medicine. Precisely the facsimile is an account, by Friedrich Zoepf, based on his longer article, of the life and work of Ulrich Ellenbob (not Ellenhob, as Dr. Carozzi spells it). The name is probably derived from Ellenhofen in Vorarlberg, Austria, about 30 miles east of Ulrich's birthplace, Feldkirch. He was educated at the universities of Vienna, Heidelberg, and Pavia, graduating as Doctor of Medicine at the last named in 1459. He then returned to his home town of Feldkirch. Later he occupied an official position as physician to the Cathedral in Augsburg, where his treatise was written. He was a devoutly religious man and paid particular attention to the religious education of his 11 children. He entered the service of the Church. He died in 1499. Three of his works were printed, four are known only in manuscript, while five others are lost. A short account of the present pamphlet from the medical point of view has been provided by Franz Koech, who claims for it the distinction of being the first work on industrial hygiene in the literature of the world. A typographical study follows from the pen of the editor, who concludes that although the work was written in 1473 it was not printed till 1524 by Melchior Rammering in Augsburg. Since the reprint itself is not easily accessible, and Ellenbob's fifteenth century Swabian is not such easy reading as modern High German, Mr. Cyril Barnard, Librarian of the London School of Hygiene and Tropical Medicine, has made a translation of the text; this occupies only eight small pages in the original, and the translation is complete.

SALE AND PURCHASE OF PRACTICES.
We have received from Mr. Percival Turner a little pamphlet which is a partial reprint of the "Hints for the Medical and Dental Professions" which he wrote some years ago and which is now out of print. These "Hints," as the author terms his excerpts, relate particularly to the sale and purchase of medical and dental practices and partnerships, and include much information given in the previous publication, when it remains relevant to existing circumstances. We may draw attention to the fourth chapter which sets out the circumstances for the employment of assistants and locum-tenents, for every practitioner knows there are many difficult positions that may arise in these relations, such as the death or bankruptcy of the principal, or the failure of one or other party to keep the terms of the contract, the misunderstanding of agreements for special services, travelling expenses, and so on. Mr. Turner gives wise counsel on these and analogous points out of his long experience.
To the skilful, subtle and noble craft of Goldsmithery of the Imperial City of Augsburg.

My willing devoted service be ready for you all. As I, Ulrich Ellenbog, Doctor of Physic, of Feldkirch, now Physician to the Dean and Chapter of Augsburg Cathedral, have observed great, saving, and remarkable things, whereof this skilful craft cometh through the fumes and vapours of the things wherewith the said craft hath to work, and people withhold only from giving advice for the service and help of the craftsmen, that they come not to such grievous harm or disease through these fumes. Also, dear craftsmen, if one of you in gilding or refining hath inhaled much vapour, so that he feeleth distressed and hurteth himself, turn away into bed and then take a good hot draught such as a large hazelnut with rue-water or speedwell-water or wine, and thus the poison will be driven of him, which hath entered the air. Then, and after gilding or refining, if ye shall after refining or gilding drink warm cowdrew, for by the warmth and heat of the cowdrew, these vapours will be driven away from ye, and ye shall hold the property that it withstandeth the poison. And new that who hath no cowdrew wine in his cellary may in a day or two hours have cowdrew wine.

Given at Augsburg the 6th day of October, 1473.

...
brief clinical note attached to it. There is a short history of the technique employed at the Middlesex since 1912, and each section of photographs is introduced by two or three pages of letterpress on the technique employed and the results obtained.

PRACTITIONERS' REGISTER OF DANGEROUS DRUGS.

We are informed that there is still some misapprehension about the requirements of the Dangerous Drugs (Consolidation) Regulations concerning the keeping of registers by medical practitioners who do not supply or dispense any of the drugs which are subject to such medical practitioner who obtains the drugs for whatever purpose is, by No. 11 (1) (A) of the Regulations, required to keep a register in the form set out therein true particulars with regard to every quantity of any of the drugs obtained by him at the time he obtains them.

STAINING SMEARS FOR THE MICROSCOPE.

There are many small pedantic practices which take up much time and might well be replaced by something simpler. Where for example, microscopic control is of decisive importance in diagnosis the usual plan is to take a smear and lay it by for further period of investigation. To simplify these operations Dr. Felice Marta, of Milan, uses an ordinary copying pencil. The smear being obtained, the tip of the pencil conveys a drop of water on to the slide beside it. In a few seconds the drop is adequately coloured by the pencil, and it is then allowed to glide over the smear which rapidly absorbs the stain. When dried, the smear shows uniform transparent in the free spaces, and especially of the stain. When dried, the smear shows uniform transparent in the free spaces, and especially

INDEX TO “THE LANCET,” Vol. II., 1931.

The Index and Title-page to Vol. II., 1931, which was completed with the issue of Dec. 26th, is now ready. A copy will be sent gratis to subscribers on receipt of a post-card addressed to the Manager of THE LANCET, 7, Adam-street, Adelphi, W.C.2. Subscribers who have not already indicated their desire to receive Indexes regularly as published should do so now.

Appointments

THOMAS, L., Glynne, L.R.C.P. Lond., M.R.C.S., has been appointed Resident Ass't, M.O., Infectious Diseases Hospital, Birkenhead.

BIRTHS, MARRIAGES, AND DEATHS.

BIRTHS.

COBY.—On Jan. 29th, at Dury St. Edmunds, the wife of Dr. J. W. E. Coby, of a son.

MARRIAGES.

Cory.—On Jan. 28th, at St. George's, Hanover Square, the wife of Dr. J. W. E. Coby, of a son.

DEATHS.