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Epidemic Encephalitis in Association with Pregnancy, Labour, and the Puerperium—A Review and Report of Twenty-one Cases.*

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INTRODUCTION.

I had the good fortune some months ago to obtain the loan of the notes of 18 patients in whom epidemic encephalitis complicated pregnancy. These patients all came under the care of Dr. Arthur J. Hall, Professor of Medicine in the University of Sheffield. My sincere thanks are due to Dr. Hall for much kind assistance and personal interest in the preparation of this Review and for allowing me to make use of his cases.

To these 18 cases I have added another three, two of which were treated at some time during the course of their illness in the wards of the Middlesex Hospital under Mr. Comyns Berkeley and Dr. Cockayne, Mr. Berkeley and Dr. D. Evan Bedford, respectively. The third case was under the care of Mr. Victor Bonney. To all these gentlemen I am much indebted.

In order to widen the outlook on the many problems which arise when a pregnant woman becomes infected with epidemic encephalitis, I have collected from medical literature some 200 cases. The total might have been greater if adequate details had been forthcoming in every case which has been reported. Of the 201 cases acute epidemic encephalitis complicated pregnancy in 171, while the remainder were cases in which pregnancy was complicated by chronic epidemic encephalitis.

In spite of the widespread interest in the disease since the

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publication of von Economo's paper[115] in 1917, there are relatively few references to its association with pregnancy, although from time to time series of cases have been reported and analysed. Jorge,[57] for instance, in 1921 reviewed 23 cases reported by various authors; Bompiani[16] in 1924 described and discussed a series of seven; others have written on various aspects of the question but as yet, to my knowledge, there has been no attempt to collect and correlate all the facts which have been observed. In this review I propose to marshal the evidence and to investigate the inter-relations of the two conditions.

Ætiology

General.

Epidemic encephalitis is believed to be due to a filtrable virus the mode of entry of which to the central nervous system is not with certainty known, but which causes in that system pathological changes peculiar to epidemic encephalitis, which is therefore a disease "sui generis."

Epidemiology.

During the ten years which have passed since von Economo's[115] first description of the disease, epidemics have frequently been reported from almost all parts of the civilized globe. In this country "encephalitis lethargica" was made compulsorily notifiable from January 1st, 1919.

In 1924 the incidence of the disease was peculiarly heavy, large outbreaks being reported in Europe, America and Japan. Great Britain did not escape; 5,036 cases were notified in England and Wales, 1,407 of which were fatal. This is by far the highest figure ever reported in these islands, the year 1925 being second with 2,634, of whom 1,372 succumbed. Of the large towns, Glasgow[21] and Sheffield[72] were those most severely affected. In the former, 398 cases were notified; in the latter, 301, representing an incidence rate of 0.57 per 1,000 of the population.

Seasonal prevalence.

The disease is more common during the colder months. The number of cases increases towards the end of the year, climbs to a maximum in the early spring and then gradually declines. This seasonal prevalence is well exemplified in the British epidemics of 1920-21 and 1923-24.

Age and Sex.

Although persons of all ages and both sexes are liable to attack, Wynne[119] has shown that on the whole there is an increased

susceptibility to infection in males, 58.4 per cent. of the Sheffield cases being of that sex. Schulze[103] goes further and states, as her opinion, that the male incidence is considerably higher than the female.

Hall and Yates[50] have shown that there is an increased liability to death in females; moreover, the number of patients of that sex infected varies directly with the severity of the disease. They classify their cases into "mild," "moderately severe" and "severe" groups; the proportion of females is lowest in the first, highest in the last group. They emphasize the fact that the increase in the female cases occurs at the lower age periods, especially below the age of fifteen years, implying that the greater the severity of the disease and the younger the patients the greater is the proportion of females.

Moreover, in the age period 25 to 35 the number of females attacked in the "moderately severe" group is exactly equal to the number of males—a matter of supreme importance since many pregnancies occur at that time of life. The importance of this observation is threefold.

Firstly, it must be remembered, when assessing pregnancy as a factor predisposing to attack; the relative increase in female cases between the ages of twenty-five and thirty-five apart from pregnancy makes doubtful the effect of the latter in increasing susceptibility.

Secondly, it is to be noticed that the increase takes place in the "moderately severe" group, in which the symptoms are better marked and the mortality higher than in "mild" cases. Allowance must be made for this when estimating the influence of pregnancy on the disease.

Thirdly, since many women become pregnant for the first time between the ages of 25 and 35 it is to be expected that the incidence of the disease is higher in primigravidæ than in multiparæ.

Pregnancy as an ætiological factor.

Authorities are not agreed about the effect of pregnancy on the incidence of the disease. Ricardo Jorge[57] writing in 1921 noted that out of 194 mixed cases in the Portuguese epidemic of 1919, five were among pregnant women, an incidence of 2.6 per cent. or about 5.5 per cent. of the total female cases (87). In Vienna during 1920-21, of 71 mixed cases, six were in pregnant women, about 8 per cent.; or 25 per cent. of the total (24) females attacked. Jorge concludes that the pregnant woman has a slightly increased susceptibility to the disease. Marinesco[68] reports two pregnancies

in nine cases—22 per cent.; Dimitz[31] five out of 20—25 per cent.; Sternberg[105] five out of 14—35.7 per cent.; Bassoe[10] one out of 10 —10 per cent.; Strecker and Willey[107] found a 28 per cent. incidence in a series of 14 unselected cases, they comment upon the rarity of such a high percentage. Pitimada[86] believes the pregnant woman is more liable to attack because of a general lowering of her resistance. Bertoloni,[12] on the other hand, in analysing 87 cases of epidemic encephalitis in association with pregnancy concludes that the pregnant woman is no more liable to the disease than her non-pregnant sister. Price[90] in a series of 78 found a 2.5 per cent. incidence.

Two cases only were associated with pregnancy out of 398 reported in Glasgow[21] in 1924. Of the 301 Sheffield[72] cases 125 were females; but only 66 in females of child-bearing age, three of whom were pregnant. Thus 4.5 per cent. of "eligible" women were pregnant; or 2.4 per cent. of the total female cases were associated with pregnancy; or one per cent. of the total male and female cases were among pregnant women.

But nine of the twenty-one cases here reported occurred in the town of Sheffield. Only three were notified in 1924, the remaining six came under observation later, on account of recrudescences or residual manifestations following a primary attack which, on account of its mildness, had escaped observation. At once a fallacy arises in the percentages arrived at in the preceding paragraph. If the six "missed" cases be added to the totals of 301, 66 and 3, the new figures of 307, 72 and 9 are deduced. The percentages that follow are:—

12.5 per cent of women of a child-bearing age were attacked.
7.2 per cent. of the total number of females who suffered from epidemic encephalitis were pregnant.

In order to avoid fallacy and to make these new figures accurate it would be necessary to add to the total of 307 all the other cases in which primary attacks were not notified but which developed obvious residua later. This clearly is impossible; but if it could be done it is highly probable, in view of the very large number of cases, that the above percentages would suffer a diminution instead of an augmentation. It is more logical, therefore, to let the series 4.5 per cent., 2.4 per cent., one per cent. stand for what they are worth. What deductions are to be drawn from this evidence?

One fact stands out above all others—those who study small series of cases find epidemic encephalitis and pregnancy associated

in a very much larger percentage of cases than those who study large numbers.

This is shown in the following table :—

Authority.	Total Cases.	Cases with Pregnancy as a Percentage.
U.S.A.[76]	864	2.7 per cent.
Glasgow[21]	398	0.5 ,,
Sheffield epidemic (Med. Res. Rep.)[72]	301	1 ,,
Jorge[57] (Portugal)	194	2.6 ,,
(Vienna)	71	8 ,,
Price[90]	78	2.5 ,,
Dimitz[31]	20	25 ,,
Strecker & Willey[107]	14	28 ,,
Sternberg[105]	14	35.7 ,,
Marinesco[68]	9	22 ,,
Bassoe,[10]	10	10 ,,

All these figures really do is to emphasize the importance of studying large numbers of cases. It would not be possible to draw a truly logical conclusion without knowing the percentage of women of child-bearing age who were pregnant at the time of any given epidemic. This figure must always be an unknown quantity and, therefore, a proper and just judgment on the point cannot be given. The evidence available, however, most certainly supports Bertoloni[12] in his conclusion that pregnancy does not increase susceptibility to the disease.

Conclusions.

1. The percentage of pregnant women infected has been variously estimated at from 35 to .5 per cent.

2. In general terms it can be said that opinions, upon the question of incidence among those who are pregnant, vary inversely with the total number of cases studied.

3. Authors who report large series are, in general, agreed that the number of pregnant women infected in any epidemic is not greater than three nor less than .5 per cent. of the total cases and conclude that pregnancy does not predispose to encephalitis.

4. There was an increased liability to moderately severe infection among females between the ages of 25 and 35 irrespective of pregnancy, in the Sheffield epidemic. This fact considered in conjunction with the incidence among the pregnant women in that epidemic (one per cent.) shows that pregnancy does not increase susceptibility to the disease.

Pathology.

Although the site of the primary infecton and the nature of the causative virus are not yet definitely known the morbid anatomy of the disease is now established on a firm basis. There is general agreement that the autopsy findings are the same in gravid and non-gravid cases. Di Francesco[39] in a recent publication confirms this statement, previously made by Sternberg.[105]

Post-mortem examination of the bodies of infants dead at birth, soon after birth, and of unborn fœtuses, have usually been negative in character. Important, and in some ways startling, findings have, however, been made on rare occasions.

The Mother.

The number of autopsies performed on those afflicted with epidemic encephalitis while pregnant is now sufficiently large to show that the pathology is the same whether the disease occurs in the pregnant or non-pregnant woman.

Macroscopic changes.

One of the most striking characteristics is the paucity of naked-eye changes.

The meninges may not show any alteration or they may appear slightly congested as in cases of Achard[1] and Bassoe.[10] Of occasional occurrence are meningeal hæmorrhages, usually of minute dimensions and situated beneath the pia mater. Such hæmorrhages were found by Couvelaire and Trillat[26] in a case remarkable for its wealth of post-mortem findings. Souques and Bertrand[110] record a particularly intense meningeal congestion. Slight, but definite, opacity of the pia mater is sometimes seen.

The meningeal congestion gives to the brain, as a whole, a tint of red deeper than the normal. The brain may be œdematous, as in Bassoe's case.[10]

On section, similar signs of congestion are evident. Variable in extent and degree the hyperæmia is almost always best marked in the grey matter of the mid-brain and contiguous parts. Often no naked-eye abnormality is discovered beyond a slight pinkness in this situation. Sometimes, however, the hyperæmia extends to the white matter and may involve the cerebral cortex and cerebellum, as in the autopsy performed by Couvelaire and Trillat[26], or to the cervical cord, as in that of Marinesco.[68]

Microscopic changes.

The microscopical changes fall into two groups:—

(*a*) Changes in the blood vessels.

(*b*) Changes in the nerve cells.

(*a*) *Changes in the blood vessels.* These are vascular and perivascular, and are found with the greatest frequency in connexion with the small venules, though occasionally the arterioles also suffer, as in Poligone's[88] case. The fibres of the vessel wall are dissected and infiltrated by numbers of cells which cause distension of the perivascular lymphatic space. This "perivascular cuffing" is the most constant and important change, but is often patchy in its distribution. It was apparently absent from Turenne's[112] case which exhibited typical symptoms of encephalitis before death. For the most part the cells are small lymphocytes with well staining nuclei, a few are large lymphocytes and some are laden with pigment granules. Here and there small microscopic collections of cells massed together are sometimes found.

(*b*) *Changes in the nerve cells.* The changes in the nerve elements themselves appear to be slight relatively to the severe and often widespread character of the symptoms. Degeneration of the nerve cells is the usual finding, but this degeneration is variable in extent and degree. Sometimes it may be limited to small groups of cells, at others it is extensive and involves considerable numbers of cells over large areas. Thus, in Turenne's[112] case no such degenerative changes were present, whereas in that of Couvelaire and Trillat[26] they were so extensive as to involve practically every part of the brain above the pons. Achard,[1] Marinesco[68] and Poligone[88] record more typical cases in which areas of degeneration were found in the usual sites. Neuronophagy may or may not co-exist. Its absence was observed by the three above named workers in their cases associated with pregnancy.

The topography of the lesions.

All writers emphasize the fact that in the large majority of cases the heaviest incidence of the attack falls upon the grey matter of the mesencephalon. The most marked changes, vascular and nervous, are usually evident in the crura cerebri, extending thence upwards and downwards with gradually diminishing intensity to the basal ganglia and pons respectively. Such cases are referred to by Poligone[88] who found the maximum abnormality in the locus niger three times out of four. Bompiani[16] likewise accentuates the importance of these parts—peduncles, basal ganglia, and pons —in the selective morbid anatomy of the disease. Achard[1] described his most intensive changes as being present in the substantia nigra, a most important region in epidemic encephalitis, for Parkinsonism is now known to be due to destruction of cells in the black substance. It seems that the disease finds a particularly suitable environment there, lingering on long after

the rest of the brain is free. The cerebral cortex is not often the site of attack. Bassoe,[10] in addition to pathological findings in more typical places, found involvment of the left frontal cortex. In a similar way cases occasionally crop up with cerebellar involvement as described by Couvelaire and Trillet.[26] Rarely is the cervical cord the seat of most marked changes. This was the case, however, in Marinesco's[68] autopsy in which the degenerative and vascular alterations became less marked as the higher reaches of the brain stem were approached.

The Child.

The records of post-mortem examinations performed on the bodies of infants born of encephalitic mothers are singularly incomplete. The frequent omission of any reference to autopsies on fœtuses or still-born infants is of sufficient significance to warrant the conclusion that the fœtal and infantile mortality are due to general causes rather than to a specific invasion of the fœtal nervous system by the virus of the disease. A similar absence of recorded post-mortem examinations on infants who have survived a few days or weeks, suggests that infection of the child by its mother is rare.

On the other hand there are two recorded cases which prove beyond all doubt that transplacental passage of the virus does occasionally occur. In 1921 Marinesco[68] published a case of epidemic encephalitis in a woman five months pregnant. She died after an illness of three weeks without delivery of her child, the absence of whose fœtal heart sounds was noted the day before her death, fœtal movements ceasing at the same time. Post-mortem examination of the central nervous systems of mother and fœtus revealed changes characteristic of epidemic encephalitis. The hyperæmia and perivascular "cuffing" found in the fœtal brain, remove all doubt as to the possibility of transplacental passage. Hall[48] refers to a similar case reported by Kononowa in Moscow. Santi[100] found typical changes in the brain of a child who died a few days after birth. Clearly it is possible that in this case infection occurred after birth.

Bassoe[10] described the occurrence of petechial hæmorrhages in the pleuræ, kidneys, bladder and stomach, in an unborn fœtus whose mother died of typical epidemic encephalitis. It is of significance that he makes no reference to any changes in the fœtal nervous system, while describing at length characteristic alterations in that of the mother. Benthin[11] describes an autopsy on an infant dead twenty hours after delivery by vaginal Cæsarean section, in which he found hæmorrhages in the choroid plexuses and hyperæmia of the meninges.

Achard[1] could discover no abnormality in the brain of a child stillborn at the sixth month. The post-mortem findings in the mother were typical.

Commandeur and Eparvier[24] refer to a case in which large meningeal and intraventricular hæmorrhages were found in an infant dead 15 hours after a precipitate labour, the latter determining the post-mortem findings.

Hallé[47] was unable to demonstrate anything pathological in the body of an infant who died with encephalitic symptoms a few days after onset at the age of four months. The mother was attacked with encephalitis while suckling the child whose symptoms appeared a few days later.

Bacialli and Scaglione[7] in a similar way record negative findings in three cases of infants dead within a few days of delivery.

Clinical Manifestations.

The Clinical Manifestations of Epidemic Encephalitis in the Pregnant Woman.

From what has been said of the pathology of the disease it is evident that epidemic encephalitis must be associated with a multiplicity of symptoms, the latter depending upon the part or parts of the central nervous system attacked, and upon the intensity of the attack in any given area. A virus which can cause pathological changes from the mid-brain upwards to the frontal cortex and downwards to the spinal cord, will necessarily give rise to many and diverse manifestations.

Following the onset and the prodromal period the disease becomes established in its acute stage which may end fatally, or from which complete recovery may take place. The acute attack may alternatively be followed by one or other of the so-called residual phenomena, or may recur after an interval of more or less freedom. Chronic epidemic encephalitis will be more properly discussed separately after the acute phase has been dealt with in all its aspects.

The Onset.

The onset may be sudden or gradual; as a rule the patient can tell with some accuracy the day, and not uncommonly even the hour at which she was taken ill. This does not mean that all the symptoms become evident at one and the same moment, but that the time of appearance of the first symptom or symptoms is recognized and remembered by the patient. Symptoms at the onset fall into four main groups between which there is considerable

overlap; they may be central nervous, gastro-intestinal, catarrhal, or general in nature.

An onset with central nervous symptoms is often marked by an overpowering desire to sleep; in other cases the first complaint is of diplopia, a symptom which may appear before or after the lethargy, while sometimes it exists in the absence of the latter and may be the sole manifestation throughout. An onset with apoplectic or epileptic attacks has been described, while in some cases delirium (cases 2 and 15), mania or other acute mental phenomena dominate the picture. Such cases at their onset may lead to a confusion with puerperal insanity.

Gastro-intestinal symptoms—vomiting, diarrhœa or constipation—may form the first evidence of the incidence of the disease. Vomiting in a pregnant patient, as in one of Robinson's[95] cases and in case 8, has to be distinguished from toxæmic vomiting of pregnancy, especially when other symptoms are absent or slow to develop. Constipation is more common than diarrhœa.

In the catarrhal group coryza, bronchitis, conjunctivitis, laryngitis and pharyngitis are all of frequent occurrence.

A common mode of onset, according to Hall,[48] is that with general malaise, headache, drowsiness, and slight fever.

The duration of the prodromal period is, like every feature of the disease, subject to considerable variation, but characteristic symptoms may be expected to appear within a week of the onset in an average case.

The acute attack.

The number and variability of signs and symptoms make it difficult to paint with clarity a picture which would fairly represent the average case. Since the days when Netter[80] enunciated his three cardinal symptoms—lethargy, headache, and fever—it has become known that not only are other manifestations equally common but that in some cases not one of Netter's triad is present. The duration of the acute attack is likewise very variable, it may last a few days or weeks, or in some cases even months. During its course symptoms come and go, sometimes changing with remarkable rapidity; the lethargy for instance may last a week or two, then disappear only to return later, perhaps to a more severe degree than before. The protean character of the symptoms and their capriciousness render classification of greater importance, greater than is its usual and more proper due. The older writers met these difficulties by describing different "types" of the disease, they spoke, for instance, of lethargic, choreatic, and hemiplegic types. Before long, as Hall[48] remarks, a state of

affairs was reached in which it became almost a recognized custom to invent a new type for each individual case. McNalty[67] in 1918 solved the problem by devising a classification of symptoms which has been widely utilized throughout the United Kingdom, and which has persisted almost unchanged to the present day. His classification was adopted by the Ministry of Health in 1922 and by Hall and Yates,[50] writing in Special Report No. 108 Medical Research Council. On this basis the symptoms fall into two main groups, general and nervous, the latter being again subdivided into positive and negative. From the point of view of severity the cases fall into three groups, mild, moderate and severe. Often the mild cases escape notice at the time, coming under observation later, on account of Parkinsonism or other sequelæ; the severe cases often terminate fatally. A case which is mild at the onset may, without warning, pass into the severe group. These and many other facts of importance will be found in the report referred to above.

General Symptoms.

The general symptoms are those of a toxic infection and include headache, fever, vomiting, catarrh of the mucous membranes, vertigo, and general achings in the limbs. Of these, headache and fever are the commonest. The former often appears at the onset and persists throughout the course. It may be of the "general infection" type, diffused widely over the calvarium, or it may be confined to the occipital region. The frequency of its occurrence has been observed by many. Smith[104] found it in 87 per cent. and Hall and Yates[50] in over 75 per cent. in the Sheffield series. It is resistant to treatment by the ordinary drugs, and occasionally persists as a residuum. Fever of some degree is usually found during the course of the disease. As a rule the temperature rises with the onset, remains moderately increased for a few days, and then falls again. Though all variations have been described the fever is usually only moderately severe. Hall and Yates[50] noted its occurrence in rather less than 40 per cent. of cases.

Nervous Symptoms.

The nervous symptoms are positive and negative.

Positive.

Positive nervous symptoms are those indicative of an exaltation of function of some part or parts of the brain and cord. The most important manifestations falling into this group are insomnia, delirium, maniacal symptoms, abnormal muscular movements,

myoclonus, disorders of the respiratory mechanism, nystagmus and neuralgic pains.

Insomnia is a very common symptom. It would appear to have increased in frequency. In von Economo's[115] original paper, published in 1917, it was noted once; whereas in the Sheffield epidemic of 1924, 50 per cent. of cases exhibited this phenomenon. It is of considerable diagnostic importance, for during the sleepless nights the other symptoms become more marked. Thus myoclonus is exaggerated, choreatic movements are more marked, delirium is accentuated. Hall[48] regards insomnia as almost pathognomonic. Alternation of insomnia by night and lethargy by day is not uncommon. del Sole[109] records it in one of his cases, Klippel and Baruk[59] observed it in theirs and it formed one of the characteristics of case 14. Robinson[95] writes of a woman who obtained no sleep for twenty consecutive nights.

Delirium is, of the positive nervous phenomena, second only to insomnia. In the Sheffield epidemic it was found in nearly 50 per cent.[72] Kirby and Davis[58] in America were struck by its frequency. It may be of occupational character, as in cases by Hofer,[56] Marinesco[63] and Poligone.[88] All varieties and grades have been described from the low muttering type on the one hand to the maniacal fury of the lunatic on the other. Hallucinations, often visual, not infrequently co-exist; or the delirium may be associated with delusions. Thus in one of the cases reported by Strecker and Willey[107] the woman was convinced, presumably without justification, of her husband's infidelity; Klippell and Baruk's[59] patient refused to believe that the child born to her a few hours before was her own.

The positive excito-motor phenomena play an important part in the symptomatology, though these again appear to have evolved with the disease. The earlier records of 1917-18 contain a relatively small proportion of cases in which myoclonus or chorea-like movements were present; whereas writers in 1919 and 1920 all over Europe reported the prevalence of myoclonic types. In the 1924 epidemic such cases were very common, more than 40 per cent. exhibiting one or other of the excito-motor manifestations.

These phenomena have a peculiar interest when viewed from the obstetrical standpoint, not because of any greater frequency of occurrence in the pregnant, parturient or lactating woman, but on account of the obstetrical diseases for which epidemic encephalitis may be mistaken. Such confusion is particularly common when convulsions, severe myoclonus or choreiform movements form the predominant feature of the encephalitis. Cases are by no means uncommon in which other symptoms

are, as it were, dominated by those of the excito-motor group; or the other symptoms may be slow to make their appearance. Thus it is that Foulkod,[38] Bompiani,[16] Mercier,[73] Kreiss[60] and Herd,[55] all record cases of epidemic encephalitis which were mistaken for eclampsia. Case 18 was admitted to the Royal Hospital, Sheffield, with the diagnosis of chorea gravidarum. A similar mistake was made by Commandeur and Eparvier[24] in their case. It has been suggested that all cases of chorea of pregnancy are in reality epidemic encephalitis, an absolutely unwarrantable assertion, but nevertheless a statement which serves the useful purpose of demonstrating how similar may be the two conditions.

The excito-motor symptoms present considerable diversity. At one end of the scale is the simple spasmodic twitching of a few fibres of a single muscle, at the other is the convulsion of an epileptic or apoplectic character. Between these two extremes are ranked all degrees of myoclonus, choreiform and choreo-athetoid movements.

In its most typical form myoclonus is painless and unperceived by the patient. The affected muscle contracts briskly and involuntarily as though stimulated by an electric current. The contractions may be limited in extent to a single muscle or to a few fibres of a muscle; they may, contrariwise, affect several muscle groups, the grouping being quite irregular and bizarre. In case 15, arms, legs and tongue were attacked by myoclonic spasms; in case 13 the twitchings affected both hands and the oral muscles; in one of Poligone's cases[88] the lower abdomen and both forearms exhibited spasmodic movements; in this case there was an associated tremor in both limbs. Less commonly the twitchings are associated with severe neuralgic pains at the affected site. This combination is more common when the myoclonus makes its appearance at onset, as in case 8. In such cases the spasms become less painful, though no weaker with progress of the disease.

Allied to the simple myoclonus described above are the more severe choreiform movements, which may closely simulate chorea gravidarum. They are most common in those cases in which the onset is marked by other positive nervous phenomena—persistent insomnia, delirium, hallucinations. After persisting with some violence for a few days, with or without concomitant myoclonus, the movements gradually cease and give place to the negative phenomenon of lethargy.

Allusion has already been made to the occasional occurrence of one or more convulsions of epileptiform nature. Such is characteristic of the more severe cases, as has been recorded by Pansera,[82] whose patient died within ten days of a convulsive onset.

Nystagmus is common, being present in some 30 per cent. of cases. It may be the usual horizontal type; sometimes better marked in one than in the other direction; sometimes coarse to one side, fine to the other; sometimes vertical, and occasionally the movements are extremely violent. In Banister's[8] case both horizontal and vertical nystagmus were present. It is interesting to note that its incidence (a little less than 30 per cent.) in the 18 cases of Hall reported here, exactly coincides with the general occurrence of nystagmus in the epidemic of which these cases formed a part. Nystagmus may or may not co-exist with other eye phenomena.

About a quarter of the cases are associated with neuralgic pains, which may or may not accompany myoclonic movements. The pain may be of great severity, and very distressing to the patient. Its site varies in different cases, but usually remains constant in its distribution in any given case.

A not uncommon phenomenon is a painful abdominal myoclonus which is liable to be mistaken for an acute abdominal condition, such as appendicitis.

Negative.

Negative nervous symptoms point to depression of function in the affected part of the central nervous system. Of these there are eight—lethargy, palsies of the oculo-motor nerves, palsies of other cranial nerves, hemiplegia, paraplegia, asthenia, amaurosis, anæsthesia.

Of all the symptoms that which most unmistakably stamps the disease is lethargy. It was this that led Economo[115] to his masterly paper and to the picturesque name which he gave to the disease. With headache and fever it formed one of Netter's[80] classical triad. In its less severe forms the lethargy is evidenced by an overpowering desire to sleep, as in a case recorded by Gullain and Gardin.[44] Often a patient apparently in a profound slumber is perfectly cognisant of the happenings around her and when spoken to replies coherently and sensibly to questions. Her mental and bodily activities are, as it were, suspended, she feels neither hunger nor thirst, and in the absence of external stimuli makes no effort to perform the ordinary functions necessary to life. Other cases are marked by a deeper degree of somnolence from which the patient can only be aroused with difficulty; in yet others coma is complete.

The degree of lethargy varies not only in different patients but shows daily variations in the same patient. Its duration is inconstant. It may last for but a few days, or for several weeks, and in rare instances for months. It may disappear, only to return

after an interval of time without recrudescence of other symptoms. It is of considerable importance to remember that lethargy, though characteristic of the disease, is not always present. Thus the Sheffield figures show a 65 per cent. incidence.[72]

All writers are agreed on the extreme frequence of ocular symptoms. This is to be expected from the pathology of the disease, the brunt of the attack being almost always borne by the mid-brain and contiguous parts. The nuclei of the oculo-motor nerves lie in the floor of the Sylvian aqueduct and fourth ventricle occupying a considerable vertical extent in the mid-line of the brain stem. The surprising fact about these signs is not their frequency but their occasional absence. Andérodias,[3] Commandeur and Eparvier,[24] del Sole,[109] Poligone,[88] Guillain and Gardin[44] all record typical and undoubted cases of epidemic encephalitis in association with pregnancy in which eye signs were wanting. Now and then cases are found in which some visual disturbance affords the only evidence of the disease. The ocular symptoms have reference to motility; disorders of the optic nerve are as rare as disorders of motility are common. Their duration is generally that of the disease and in most cases their disappearance heralds recovery. Occasionally, however, their onset is delayed until later, and in rare cases they appear as sequelæ. All varieties of ophthalmoplegia have been described; the third pair of nerves is more frequently affected than the fourth or the sixth. Diplopia was found in six out of 13 cases by Poligone;[88] it was present in 10 out of 21 cases here recorded. Its frequency is roughly equal to that of nystagmus (Bollock).[120] Ptosis, unilateral or bilateral, may be present as the only ocular manifestation, or may co-exist with other eye signs. All varieties of pupillary disorder have been seen—inequality, loss of reaction to light, to accommodation or to both, myosis, and mydriasis. Inequality of the pupils is recorded in case 13, it was observed by Novaes and Souza[81] in their patient; in Hofers[56] case the pupils did not react; Gaujoux and Vincent[114] report pupillary inequality; examples of mydriasis are found in cases of Robinson,[95] del Sole[109] and di Francesco.[39]

Of the other cranial nerves the seventh, fifth, twelfth and tenth are those most liable to attack, in that order of frequency.

Facial paralysis, usually incomplete and unilateral, may be bilateral and complete. It may appear early, as in case 15, or late as in case 17, in which it came on some three years after the primary attack. Forget,[36] Bompiani,[16] Robinson[95] and Kreiss[60] all speak of this symptom, and in all these cases only one side of the face was affected.

It is not necessary to dwell further upon the negative manifestations. Let it suffice to note the possibility of the occurrence of hemiplegia, paraplegia, asthenia, amaurosis and anæsthesia.

The Influence of Pregnancy on Acute Epidemic Encephalitis.

Opinions are at variance about the effects of pregnancy on the acute attack. Some believe that the disease runs a more serious course when it occurs in pregnant women, others that the course during the acute stage is the same in gravid and non-gravid patients.

Before arriving at a decision on this very important question it is necessary to consider in turn the mortality, the symptomatology, the effect of emptying the uterus and the question of increased susceptibility to infection during pregnancy, any or all of which may help towards elucidation.

(*a*) *Mortality.*

Hall[48] states that the average mortality in all cases of epidemic encephalitis is about 27 per cent., a figure which is almost universally accepted, and which finds confirmation in the Registrar General's returns for 1924 when 28 per cent. of those infected died. It must, however, be remembered, as Hall points out, that any such figure is too high on account of the large number of mild or abortive cases—"formes frustes" of the French—which escape notice. But since concern here is chiefly with the relative mortality in pregnant women, this factor, affecting alike gravid and non-gravid groups, assumes diminished importance.

When enquiry is made into the opinions held on the question of mortality in pregnancy great differences are found, the estimated death rate varying from four per cent. in the present series of 21 to 70 per cent. in the 10 cases reported and analysed by Sebastiano di Francesco.[39] Certainly the former series is in many ways unique and many of the cases both of Hall and Berkeley were admittedly mild, coming under observation on account of residual phenomena. Even so divergence to such a degree is not accounted for satisfactorily.

French authors are almost unanimous in the opinion that the mortality among pregnant patients is particularly high. Reference need only be made to the writings of Jorge,[57] Vincent et Gaujoux,[114] Robinson[95] and Fort,[37] when it will be found that, though differing in minutiæ, the general consensus of opinion among them is that the death rate is raised. In Austria and Germany a like

opinion prevails, and is held by Dimitz,[31] Hofer[56] and Tropl.[111] The Italian authorities do not agree. Di Francesco,[39] on the one hand, is appalled at the outlook for women afflicted when pregnant, while Bertoloni,[12] on the other, can find little cause for a grave prognosis to the mother as far as the encephalitis is concerned; between, in the no-man's land, stands Bompiani[16] who quotes a moderate mortality figure. What information is forthcoming from the United States of America[76] is on the optimistic side, while in our own country the published figures and views indicate a neutral state.

Collecting and presenting these current opinions in tabular form :—

Authors.	Year of Publication	Place of Origin.	Total Cases.	Mortality
Jorge[57]	1921	France	23	60 per cent.
Robinson[95]	1921	France	23	60 ,,
Vincent et Gaujoux[114]	1921	France	12	66.6 ,,
Fort[37]	1926	France	10	50 ,,
Dimitz[31]	1920	Austria	5	40 ,,
Tropl[111]	1921	Austria	7	70 ,,
di Francesco[39]	1926	Italy	10	70 ,,
Bompiani[16]	1921	Italy	15	46 ,,
Bacialli & Scaglione[7]	1921	Italy	5	60 ,,
Bertoloni[12]	1924	Italy	87	40 ,,
U.S.A.[76]	1922		24	16 ,,
Ministry of Health[76]	1922	Great Britain	50	44 ,,
Author's series—Hall, Berkeley, Cockayne, etc.	1928		20	5 ,,
"Collected cases"	1928		170	42 ,,

The last group refers to those cases collected by the author from every source open to him, but it does not include the 21 cases reported here. Further details of those 170 cases will be given later.

What is there to explain these variations?

Firstly, there is the error due to small numbers, occasioned, in the years gone by, to a paucity of material; the mortality in the groups quoted above varies inversely with the number of cases studied. Secondly, there is the error of repeating cases; an example will make this clear. Jorge[57] in analysing 23 cases finds a mortality of 60 per cent.; Robinson[95] in employing the same number finds an identical mortality; but 10 of Robinson's cases were previously quoted by Jorge; if these 10 be subtracted from Robinson's 23 the mortality among the remaining 13 is 45 per cent.! If now these 13 new cases by Robinson be added to Jorge's series the

average death rate is about 52 per cent.! Thirdly, there is a factor difficult to gauge but nevertheless present and acting; this has relation to the date at which the cases were reported and to the country from which they were derived. Earlier writers find a heavier mortality than later; French higher than British. This is due in part to a variation in virulence and in part to the fact that in 1920 and 1921 the true encephalitic nature of less severe cases was not recognized. Fourthly the corresponding (as regards time and locality) mortality in non-pregnant women is not always quoted. Even if it is, its validity is sometimes questionable, for to collect from all parts of Europe the results in a number of pregnant women and compare the death rate in these with that in a mild local epidemic begs the question. Admittedly, sometimes the mortality among pregnant women does exceed that in the non-pregnant but on other occasions the two correspond. Dimitz,[31] for example, remarking on the greater severity of the disease in pregnant women finds a mortality of 40 per cent., but according to his own showing the mortality in the non-pregnant women in Vienna at that time was the same—40 per cent. Finally there is the ætiological factor emphasized in the Ministry of Health's Report[76] and in the Medical Research Council's pamphlet[72] dealing with the Sheffield outbreak, commented upon by Schulze,[103] overlooked by all others save Hall,[48] who points out that there is an increased liability to death in females, quite independent of pregnancy.

What part each of these factors plays in determining the diversity of expressed opinion cannot be estimated. The possibility of their activity bespeaks caution and makes dogmatism unsafe. That the virus differs in epidemics is well known, that it varies in its most marked effects from time to time and from locality to locality is established. May not these variations account in part for many of the differences in reported mortality?

(*b*) *Symptomatology.*

That most important index of severity—mortality—being unconvincing and equivocal, other evidence must be sought. If it could be asserted dogmatically that the large majority of cases attacked during pregnancy were symptomatically more severe, then the contention that pregnancy exacerbates the disease would be upheld. If this were true a higher mortality would certainly be expected, though clearly the cases might run a course in general more severe, yet not more frequently pass to a fatal termination.

Turning first to the cases here reported, the large majority of which (1—18) came under the care of Hall in Sheffield. it is

impossible to do better than quote his own opinion (personal communication). "Such cases as were under immediate observation throughout presented the usual variations seen in non-pregnant cases. Some were severe, some medium, some mild. In one case the attack was so slight that its exact date could not be ascertained. The symptoms were similar in kind, combination and duration to those seen in non-pregnant persons." Of these cases what more need be said? The authority is sufficiently high to command acceptance. If, however, there be any unbeliever all he need do is to analyse the cases and compare them, symptom for symptom with non-pregnant cases in the same epidemic. He will find a remarkable correspondence in almost every particular. Symptoms which are common in this series will be found to be common in the epidemic as a whole, they form indeed an almost exact replica in miniature of the Sheffield outbreak, a fact not altogether unremarkable and of great significance when it is remembered that there are only 18 of them.

The outstanding symptoms in the epidemic as a whole were headache, ocular palsies and lethargy. Headache, it must be agreed, is not frequently referred to in Hall's series of pregnant women, but this is doubtless due largely to the fact that he did not have an opportunity of seeing all the patients during the progress of the acute attack; it is a symptom which, unless especially marked, may easily escape notice, being overshadowed by more spectacular phenomena. At all events, whereas it occurred in more than 70 per cent. of the 301 Sheffield cases,[72] it is mentioned in only 35 per cent. of those associated with pregnancy. On account of the foregoing considerations no great weight need be attached to this apparent discrepancy, in any case if a conclusion were to be forced it would be that headache is less common in cases of acute epidemic encephalitis when associated with pregnancy. Even if this conclusion could be upheld its importance would remain debatable. Lethargy and ocular palsies show a close correspondence in the two groups, the former occurring in rather more than 70 per cent. of the pregnant women; in rather under 70 per cent. of the non-pregnant; the latter in somewhat under 60 per cent. in the non-pregnant women, more than 60 per cent. in the pregnant. About half of the three hundred and one cases notified in Sheffield suffered from each of those two symptoms. Passing to the less common phenomena attention has already been drawn to the fact that nystagmus was present in 18 per cent. of cases in both series, while fits in the same way occurred in five per cent. of each; the percentages for myoclonus are 15 per cent. in the general, and about 16 per cent. in the pregnant group.

These cases indubitably show that, with the single exception of headache, there is a very close correspondence in symptomatology between pregnant and non-pregnant women, sometimes the similarity is mathematically exact. To be added to this is Hall's statement, reproduced above, that in respect of symptom combination and duration the course of the acute attack in these cases presented no noteworthy differences from the symptomatology in non-pregnant women.

Proceeding to a consideration of the current opinion on this subject we find that those who have studied the matter appear to be divided into three groups. Some are confident that pregnancy acts in what may be termed a "generally aggravating manner," all symptoms being better developed and of greater severity; others hold that pregnancy causes an exaggeration of certain special symptoms; yet others deny any influence at all. Many, indeed most, do not trouble to draw a distinction between increased mortality and aggravation of symptoms. They are satisfied that the death rate in pregnant women is unusally high, and assume from this that the course must be correspondingly more severe. Certainly the one belief fosters the other. Aggravated symptoms and enhanced mortality necessarily go hand in hand but if that enhancement be not admitted it becomes essential to fall back on other evidence which would be furnished in part, as has already been suggested, by an answer to the question, "do the symptoms of acute epidemic encephalitis in pregnant women differ in degree or kind from those manifested by non-pregnant women attacked under similar conditions of locality, age and time?"

In 1920 Dimitz[31] emphatically answered this question in the affirmative. He described a series of 20 cases, five of which were pregnant, these five suffered to a considerably greater extent than the others. Two of the five died, a mortality of 40 per cent.; according to his own calculations the mortality in non-pregnant women at that time in Vienna was 40 per cent. Evidently these cases can be used in support of either view! Without doubting the accuracy of these observations it can be argued that the severity of symptoms in the five patients was a coincidence. The number is small, many patients in that epidemic suffered even more severely than those five, many others suffered less, the fact that the mortality was the same in the pregnant and non-pregnant groups proves a general similarity between the two. Amreich,[2] Waldstein,[118] Latzko,[62] Sternberg[105] and Kreiss[60] all concur with Dimitz,[31] but their concurrence rather takes the form of reports on pregnant women under their care in whom the disease was of severe degree or who benefitted by evacuation of

the uterus. Thus Sternberg's[105] five cases were all fatal, but both of Kreiss's[60] recovered after artificial termination of pregnancy; one of these cases was severe, the other only of moderate severity. To argue that Kreiss's cases prove an aggravation during pregnancy is surely without justification, because they were no more marked than many others in that epidemic. Yet they have not infrequently been quoted in defence of the belief that pregnancy exerts an untoward influence on the disease, as, for example, by di Francesco.[39] Whether the effect of emptying the uterus shows such influence is another matter and will be discussed later, di Francesco[39] does not advance any argument on these lines. Fino and Fubini[35] incline to the view that gestation is an adverse factor, but again their two cases made a good recovery after artificial termination, a fact on which they lay emphasis and which will be referred to again; their cases would legitimately be classed as severe though not of the greatest severity. Marinesco[68] in 1921, without being too dogmatic, gave it as his opinion that pregnancy should be regarded as a cause for grave prognosis, but he argues from a conviction that the mortality is higher in these cases. Jorge,[57] Achard[1] and Robinson,[95] in the same way and at about the same time, came to a similar conclusion for the same reason. Alfons Müller,[77] addressing an audience in Frankfurt during the year 1923, expounded his belief in this view. To be added to its supporters is di Francesco[39] who bases his thesis however, entirely on the mortality rate and certain other factors; he admits that pregnancy did not appear to be the cause of any special phenomena and that it did not alter the symptoms which generally make up the clinical picture of the disease.

Among those who believe that pregnancy acts in a special, as opposed to a general, manner is Poligone[83] who in 1926 concluded that the adverse influence found expression chiefly in a shortened prodromal period, a temperature which rises early and remains high, augmented blood-urea concentration and increase of glucose in the cerebro-spinal fluid. He does not deny that his findings require verification and investigation on a larger number of cases. In criticism of a very admirable piece of work it can only be stated that Poligone's opinions do not receive support from a review of the literature. The prodromal period is variable in pregnant as in non-pregnant women, the temperature likewise presents no constant variations, while the biochemistry of the disease is scarcely yet established on a sufficiently secure basis to admit of discussion in special relation to pregnancy. When the urea content of the blood is raised who can say that it is due to the disease and would not have taken place in that particular pregnancy apart from its

association with encephalitis? This matter, in any case, is out of place here, belonging to the sphere of possible influence of the disease on pregnancy rather than those of the latter on the disease. Herd[55] concludes that pregnancy alters the onset, early symptoms and severity; really his cases were not atypical apart from an associated albuminuria and other evidence of toxæmia of pregnancy. Fabre[34] thinks there is an exaggeration of the lethargy when pregnant persons are attacked; Theodore Haultain[51] made a similar observation in reporting a case in Aberdeen in 1921. Hall draws attention to the aggravating effect of the pregnancy on those cases (case 18) which are associated with painful abdominal myoclonus.

It would be possible to quote case after case of encephalitis in association with pregnancy which has run a severe course and which, in its reporter's opinion, proves the point for protagonists of the "adverse influence" school, but isolated instances, be they never so numerous, are not in fact proof when similar examples can be produced on the opposite side.

In the Ministry of Health Report,[76] 1922, a series of 50 cases is reviewed and the conclusion reached, contrary to expectation, that they ran much the same course as the others. Hall[48] in 1923 expressed agreement with this conclusion—Benthin[11] in 1920, had previously been unable to establish a worse prognosis though he believed the effect of encephalitis on pregnancy to be unfavourable. Pollastoni[87] was unable to find any peculiarities in pregnant patients, but nevertheless advised a guarded prognosis. Bertoloni[12] in a careful analysis of 87 cases concluded that the course of the disease is the same and the mortality no different. This author has been criticized very freely and perhaps a little unkindly by di Francesco; so anxious is the latter to explain why the disease is more frequently fatal that he takes it for granted that any one who suggests a contrary opinion must *ipso facto* be wrong. Having begun with that assumption he does not find it difficult to prove his case. Patek[84] is of Bertoloni's[12] opinion . Tropl[111] regards the labour, not the pregnancy, as the aggravating factor.

The belief in symptomatic aggravation during pregnancy has, therefore, its opponents as well as its supporters; as might have been expected from a previous study of the mortality the evidence is conflicting. There are two diametrically opposed schools, each with its own "credo"; each convinced unflinchingly of the truth of its own tenets. It is interesting to notice how shrewd observers, like Jorge,[57] express opinions which show that they regard both sides with a certain healthy suspicion. That writer is slow to draw conclusions from what he regards as too few cases, and is

careful to state that he awaits further material before giving his final dictum, in the meantime advising a guarded prognosis.

(*c*) *The influence of the labour and the effects produced by evacuation of the uterus.*

Two considerations arise under this head. Firstly it is desirable to attempt to form an estimate of the effect of the labour itself upon the course of the disease. Do the stress and strain of labour cause in these patients any change for the worse? Secondly, does the removal, natural or artificial, of the products of conception produce an improvement by enabling sufferers the better to combat encephalitis? Upon the answers to these two questions an estimation of the influence of pregnancy on acute epidemic encephalitis partly depends, and their importance with regard to the question of treatment can scarcely be over-estimated. If a uniform improvement after delivery could be shown to be the rule it would be right to conclude that pregnancy was an aggravating factor, in which case artificial termination would have to be advised in all cases.

So far as the cases reported here go the answers to both questions are in the negative, at any rate as regards the progress of the acute attack. In cases 2, 6, 11, 13, 14, 15, 16, 17, 18 and 19 the labour certainly did not play any part, for better or for worse; cases 4 and 8 were both submitted to Cæsarean section, and both recovered though the former (4) had intractable and persistent hiccough after operation, upon which Hall makes special comment. Their recovery cannot with honesty be attributed to this treatment. The labours did not influence cases 1, 3, 5, 7, 9, 10, and 12 in the sense that the acute attack recurred or became worse thereafter; cases 1, 3, 5, 7 and 12, it will be noted, were attacked during the first three months of their respective pregnancies, case 10 at the eighth month and 12 during the last week. The characteristic common to these patients is that they all developed Parkinsonian manifestations which appeared to date from soon after the confinement. Now this is a matter of some moment and will, therefore, be relegated to a special section which will deal with the several aspects of Parkinsonism in its relationship to pregnancy. Suffice it to remark here that in no case does labour itself appear to have provoked aggravation of the acute phase of the disease and that benefit does not seem to have accrued to any patient as a result of uterine evacuation, whether natural or artificial.

Just as there are two schools holding opposite views upon the question of symptomatic exaggeration during pregnancy so are opinions divided as to the effect of labour on the disease. Every

possible eventuality has been covered in the published reports of cases, which fall into three main groups:

(i) Those in which the labour appears to have caused aggravation.
(ii) Those which have improved after evacuation of the uterus whether by natural or artificial means.
(iii) Those in which the labour does not appear to have had any influence on the disease.

(i) *Those in which the labour appears to have caused aggravation.*

That a change for the worse has sometimes become apparent immediately after labour need not be a matter for surprise, indeed it is surely more remarkable that this change is as inconstant as it appears to be, both from a study of the present series and from numerous past publications in many languages. It must not be forgotten, however, that though labour, with its necessary demand for the expenditure of maternal energy, might reasonably be expected to act detrimentally, yet the fact that after expulsion of the fœtus one of the calls upon the mother's resources ceases to be made, counterbalances the untoward effects produced by the efforts necessary for the delivery. It is impossible to estimate to what extent each of the two factors acts and a further complication arises in connexion with lactation, which clearly might, by its demands, help to render worse the patient's plight. To be added to these three unknown quantities is a fourth—the numberless variations of the disease itself. That considerable confusion should exist is, therefore, to be anticipated, neither can uniformity be expected.

The cases in this first group may be further subdivided into three. Firstly, there are those which went steadily down hill after delivery; secondly, there are those which improved for a time after expulsion of the fœtus but in which improvement was transitory; thirdly, those which improved after a transient exacerbation. Jorge,[57] on the whole, adheres to the belief that the labour aggravates the encephalitis; Benthin[11] is a more staunch supporter of this view and with his name may be coupled that of Tropl,[111] and Bar[9] prays that the onset of labour may be delayed until the acute stage is over. Mercier, Andrieux and Mlle. Bonnaud[73] record a case in which labour appeared to act as an aggravating factor. Fort[37] regards onset just before or just after the confinement as an omen of evil portent and refers to a case of Répond[94] in which death took place during labour. But in all these cases, it is open to argument whether or no the disease would

have run a similar course had labour been delayed or the patients not even pregnant. The onset of encephalitis occurred sufficiently near the dates of labour and the general trend was sufficiently well marked downwards before then to make it extremely difficult to estimate the part played by labour in determining the subsequent course of the malady. It may be remarked that all the pregnancies went to term except one of Benthin's[11] cases in which labour was premature at about the sixth month. For present purposes this may be discounted since it does not affect the point at issue.

Banister,[8] Herd[55] (2) and Commandeur and Eparvier[24] have reported cases which showed a transient improvement after the uterus had been emptied. With the exception of one patient of Herd's[55] all the others died within twenty days of their confinement in spite of an amelioration in symptoms immediately thereafter. Banister[8] induced labour in his patient at the thirty-eighth week with bougies, the others were natural and full time deliveries. The explanation of this sub-group is not easy unless it be that labour initiates or aggravates changes which take time to become clinically apparent.

It is more easy to understand cases like those of Schulze[103] and Haultain[51] in which the symptoms became augmented for the few days following delivery and then began to show signs of abatement. Here it would seem that the transient aggravation caused by labour was more than counterbalanced by the beneficial effect of uterine evacuation.

(ii) *Those which have improved after evacuation of the uterus, whether by natural or artificial means.*

That improvement has taken place after fœtal expulsion or removal is at once admitted. Pollastroni,[87] Amreich[2] and Pitimada[86] record and comment upon this in cases which have been delivered naturally, and other similar references are not wanting; to be included in this group are those cases which improved after transient exacerbation. *A priori* it would seem, then, that beneficial effects would result from the termination of pregnancy in these patients more especially if one of the rapid means of emptying the uterus were adopted, thereby securing the maximum of benefit with the minimum of harm. Considerations of this nature led Dimitz[31] in 1920 to try the effect of Cæsarean section. He was rewarded by considerable success in his case, the patient recovering from the disease with great rapidity. Hofer,[56] Latzko,[62] Stursberg,[108] Kreiss,[60] di Francesco,[39] Price[90] and Fino and Fubini[35] have similarly described cases in which immediate improvement has followed termination of pregnancy either by

rupturing the membranes during the early months or Cæsarean section in the later. The total number of cases is nine and in some of these recovery was sufficiently slow to make very questionable the assumption that it was due to the treatment. Numerous observers have been unable to find any effect on the disease as a result of active obstetric measures. Santi,[100] Marinesco,[68] Jorge[57] Benthin,[11] Foulkod[38] and Banister[8] all record cases in which no benefit accrued; out of 14 artificially terminated pregnancies six patients died according to Bertoloni;[12] moreover di Francesco[39] had a failure as well as two successes.

The position may be epitomized by saying that athough improvement has followed uterine evacuation, both natural and artificial, the weight of evidence goes to show that such improvement is rather exceptional; and save for certain members of the German school, notably Hofer,[56] authorities are unanimous in the opinion that benefit does not usually result from emptying the uterus.

(iii) *Those in which the labour does not appear to have had any influence on the disease.*

The large majority of cases may justifiably be included in this, the third and last group. With the reservation that some of the patients first showed signs of Parkinsonism soon after the confinement, all of the twenty, in which pregnancy and the acute attack coincided, reported here would be so classified. The same conclusion was reached in the Ministry of Health pamphlet[76]; Marinesco,[68] Poligone[88] and Robinson[95] are all sceptical about aggravation due to labour. Di Francesco[39] and Bertoloni[12] concur, the former in spite of twice noticing improvement after induction in his own series. Harris,[52] Neal,[79] Santi,[100] Valente and David,[57] Poligone,[88] Dimitz,[31] Gaujoux and Vincent,[114] Garnett and Washington[40] and numerous others have recorded cases which recovered without noticeable change in either direction at the time of labour or the puerperium. Many other cases have passed to a fatal issue without any particularly noticeable exacerbation at the time of the confinement. Examples will be found recorded by Robinson,[95] Putnam,[91] Répond,[94] Dimitz,[31] Tiago d'Almeida,[57] Novaes and Sousa,[81] Audrey and Froment.[6]

The influence exerted by labour on the course of the disease is not yet clear, neither do the effects of artificial uterine evacuation appear to be either constant or consistent. The evidence on both these very important questions is still conflicting. In the majority of cases the disease once established runs its course onwards regardless of labour or the fact that the uterus has been emptied;

in a few the confinement appears definitely to have aggravated the disease, while in a few others the removal or expulsion of the fœtus seems to have improved the state of the mother's health. These results, discordant as they seem, need not give cause for wonder; let it be admitted that there are three groups of cases, some unaltered, some worse, some better, as a result of delivery. The relative part played by the various factors at work cannot be estimated but the suggestion is that in the first group the encephalitis is either so severe or so mild that no influence is apparent as a result of labour; in the second the calls of labour lower the general resistance sufficiently to allow the encephalitis to progress at a greater rate; in the third the removal of demands made by the growing fœtus on its mother correspondingly increases the general resistance, with a diminution in the nervous symptoms. When regarded in this light the discordance does not seem so marked and after all there is no reason why all cases should correspond; because one case or one group of cases is adversely affected by certain circumstances there is no reason why another, or another group, should show the same affection.

Returning to the general problem concerning the effect of pregnancy as a whole upon epidemic encephalitis, the fact that improvement after the uterus has been emptied is a comparatively rare phenomenon, considered in conjunction with a mortality which has not been definitely proved to be raised and a similar symptomatology, suggests the conclusion that the acute stage of the disease is not affected by pregnancy. The severity is rather dependent upon other ætiological factors and particularly upon the virulence in any given epidemic.

(*d*) *Predisposition.*

It has already been shown that pregnant women are not unusually susceptible to an attack by the virus of epidemic encephalitis. If the converse were true it would probably, though not necessarily, follow that pregnancy exercised an influence for the bad. Is the converse of this rider also a truism? Can it be argued that because pregnancy does not predispose to attack it, therefore, has no influence on the disease? The answer to this must certainly be in the negative both on theoretical and practical grounds. Theoretical because pregnancy by lowering the general resistance might easily cause the encephalitis to assume a more severe form without rendering the patient more liable to primary attack; practical because other diseases are known to which pregnancy does not predispose but upon which it exercises an untoward influence, e.g., measles, smallpox, pulmonary tuberculosis .

What may be described as a "lack of predisposition" is not, therefore, of any importance in assessing the effects of pregnancy on the disease. This factor can be discounted in balancing the *pros and cons*.

Summary and conclusions.

An attempt has been made to estimate the influence of pregnancy on the course of acute epidemic encephalitis. Mortality, symptomatology, the effects of uterine evacuation and the question of predisposition are considered in turn.

(1) *The mortality* among pregnant women infected by the virus of the disease has been variously estimated at from five to seventy per cent. The variations are to be explained on grounds which have reference to the number of cases studied, the year and country in which that study was conducted and the known variability in virulence.

On the continent of Europe opinion inclines to the view that the mortality is raised in cases complicated by pregnancy, the quoted figures usually being from fifty to sixty per cent.

In GreatBritain it is admitted that there is an increased liability to death in females irrespective of pregnancy and the mortality among those infected while pregnant is not found to be raised.

Only five per cent. of the author's cases proved fatal.

In a series of one hundred and seventy cases collected from the literature and excluding the author's series, the mortality is equivalent to about 42 per cent., a rate in all probability not in excess of that among all persons attacked under similar conditions of age, sex and locality. Determination of the latter is impossible on account of the wide distribution of these cases.

(2) *The symptomatology* in Hall's group of 18 cases is shown to be almost identical with that exhibited by non-pregnant patients in the same epidemic. A survey of the literature shows that in general there is a close correspondence between gravid and non-gravid women. There is no valid evidence to justify the conclusion that pregnancy is the cause of an altered symptomatology either general or special.

(3) *Labour* in some cases causes a marked change for the worse; in others an improvement follows delivery of the child; in the third and largest group there is no noticeable alteration in the condition attributable to this factor.

(4) *Predisposition* is denied relevance in this connexion.

The evidence then, taken as a whole, shows that the course of acute epidemic encephalitis is not altered in a woman by the fact that she is pregnant.

The Influence of Acute Epidemic Encephalitis on Pregnancy, Labour and the Puerperium.

(*a*) *On Pregnancy.*

Modification in the natural course of pregnancy produced by any disease might be shown in one or more of three ways. In the first place it might be shown by spontaneous interruption before term, in the second by diminution in hepatic and renal activity—toxæmia of pregnancy—, in the third by the occurrence of fœtal death before term. These three are obviously interrelated, particularly the first and the third; it is admittedly difficult to decide in many cases whether miscarriage is due to intra-uterine death of the fœtus or whether death is due to miscarriage. It is, however, convenient for present purposes to keep the two distinct, inasmuch as fœtal death if at all common would be of value in determining the question of a transplacental passage of the virus and the existence of congenital epidemic encephalitis.

Of the series of 21 cases little need be said. The only two which did not proceed in the ordinary way to natural labour at term were those upon which Cæsarean section was performed (cases 4 and 8). In no case was the pregnancy associated with toxæmia; no patient miscarried; neither did the onset of labour in any of the patients occur at a date which might not ordinarily have been expected; the children were all born alive. These facts speak for themselves, showing most conclusively that, so far as these cases are concerned, the attack of encephalitis made no difference to the natural course of pregnancy.

This is in agreement with the conclusions pronounced by the Ministry of Health in 1922 when only five miscarriages were reported against 24 normal full time deliveries.

Very different are the views of a considerable number of Continental authorities. In 1921 Jorge,[57] in an analysis of 23 cases, concludes that the commonest mode of termination is by spontaneous interruption of pregnancy followed by death of the mother, which usually takes place within a week of delivery. But only five of the 23 miscarried, just over 20 per cent.; according to Galabin the usual proportion of miscarriages to full time deliveries is as one to five, that is to say, 16.6 per cent. of all pregnant women miscarry. Di Francesco,[39] writing in 1926, expresses the belief that premature labour in the last two months of gestation is of common occurrence when the acute attack of encephalitis occurs during pregnancy. This belief he founds on "the experience of a great number of authors;" his own cases he has to admit do not conform, for only one out of the 10 miscarried; if the three he

treated by induction are excluded altogether the total is reduced to seven; one miscarriage in seven pregnancies is still well within Galabin's limit. Among di Francesco's authorities are Santi[100] and Baccialli and Scaglione.[7] Now Santi[100] wrote of two cases at Siena in March 1920: one of these was delivered prematurely at the eighth month, and in his opinion the onset of premature labour was due entirely to the disease, the virus of which he thinks stimulates the special nerve centres—thereby causing uterine contractions. Baccialli and Scaglioni[7] had two premature labours in five cases; these authors advance the theory that uterine contractions are brought about by the high temperature, di Francesco himself thinking that prematurity is due to the toxæmia produced by the virus of epidemic encephalitis. Fino and Fubini[35] regard miscarriage or premature labour as indicative of the severity of the disease. Bertoloni[12] in 1923, after a review of 87 cases, came to the conclusion that premature birth is about twice as frequent as delivery at term. Unfortunately the details of these cases are not forthcoming and criticism cannot therefore be offered. It is of interest to compare the last named series with that of Poligone,[88] who, in 1926, came to a similar conclusion, namely, that half the cases miscarry; Poligone[88] had 11 miscarriages in 19 cases. Veksin[113] in Russia, Alfons Müller[77] in Germany, and Cova[27] in Italy uphold the teaching that pregnancy is frequently interrupted; Tropl[111] reports five miscarriages in seven cases. Robinson[95] in France records results which are not in agreement with what appears to be the great body of Continental opinion. That writer described 13 cases without a single miscarriage though seven proved fatal before delivery.

One hundred and thirty-nine cases have been found infected during pregnancy in which the fate of the products of conception is known.

These may be classified in the following way:

64 were delivered at term.
30 died without being delivered.
25 were natural premature deliveries.
19 were artificially delivered.
1 was a case of extra-uterine gestation.

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("Delivery at term" does not necessarily imply that the child was alive and healthy. Confinement at term indicates broadly that the disease was in those cases without influence on the pregnancy).

Excluding the 19 cases in which pregnancy was artificially terminated and the one in which the gestation was tubal, it appears that rather more than half the remainder proceeded to delivery at term, about a quarter died without being deliverd, and rather less than a quarter delivered themselves spontaneously before full time.

In the first and largest group, therefore, there was no interference with the course of pregnancy; in the second group, in which all the patients died, there is a similar absence of evidence to show that encephalitis affects pregnancy. The third group, though relatively small, is sufficiently large to make improbable the hypothesis that the miscarriage or premature labour was a pure accident connected in no way with the disease. This is borne out by an examination of the following figures :—

Premature deliveries = 25.

Fatal termination in 11
Non-fatal in 14
Mortality 44 per cent.

Deliveries at term = 64.

Fatal termination 11
Non-fatal termination 53
Mortality 17 per cent.

In the light of this evidence interference with pregnancy in the more severe cases cannot be denied, and a working rule may be formulated with regard to the outcome of the pregnancy when affliction is serious. It may be said that the most severe cases die before delivery, in the least severe gestation proceeds to term, while in the intermediate group premature delivery is to be expected.

Intra-uterine death of the fœtus before term has from time to time been reported (Voron and Pigeaud,[117] Répond,[94] Robinson[95]). It is of considerable rarity though an established phenomenon. Because in some cases the death of the embryo has coincided in point of time with the occurrence of severe encephalitic symptoms, it is concluded that such death was due to the disease and the general conclusion with regard to the effect of severe epidemic encephalitis on pregnancy is upheld.

Leaving for a space this question of miscarriage and passing to that relating to toxæmia of pregnancy, Benthin[11] in 1920 recorded

two cases in which the latter was present. He therefore concluded that pregnancy is adversely influenced. This association, however, is not common; true enough, occasional cases are found throughout the literature, but not in sufficiently large numbers to admit of any far reaching conclusions. Moreover, it must not be forgotten that epidemic encephalitis is itself associated with a toxæmia as evidenced clinically by the fever and other general symptoms; pathologically by the kidney and liver changes which have been found post-mortem in cases not associated with pregnancy. It is therefore not just to conclude that every patient with albuminuria has in addition to her other troubles a toxæmia due to the pregnancy and not to the encephalitis. The chief importance of such cases lies in the diagnostic difficulties with which they are beset.

(*b*) *On Labour.*

On this point complete agreement has been reached. It is universally admitted that labour so far from being difficult is exceptionally easy in cases complicated by acute epidemic encephalitis. An extreme example of this was witnessed by Gaujoux and Bertrou[41] whose patient went into labour while in hospital and delivered herself of a full time child without anyone being any the wiser till the infant was found dead of asphyxia in the mother's bed some time after birth. This case is all the more remarkable in that the patient was a primipara and the baby well developed. It would seem as though the senses of such patients are dulled and their capacity of perceiving pain abolished, or at least diminished. Anæsthesias are not uncommon in connexion with epidemic encephalitis, and it has been suggested by Jorge[57] that there is a special anæsthesia in these patients preventing the receipt of painful stimuli. Victor Bonney remarked on the anæsthesia of the external genitalia after confinement in case 21. There is a complete absence of any obstetric accidents both from the cases reported here and from those throughout the literature. Occasionally assistance by the forceps has been rendered necessary by inadequacy of the maternal forces. Such cases are very exceptional and the patients have been primigravidæ. The women often remember nothing of their labour, as in Klippel and Baruk's[59] case to which reference has already been made.

(*c*) *On the Puerperium.*

Like labour the puerperium is almost always devoid of complications other than those directly connected with the condition of the central nervous system. The only noteworthy exception

appears to be the occasional occurrence of retention of urine after labour. Schulze[103] first stressed this point; it is not improbable that the bladder inertia is due to a central paralysis resulting from the disease.

Summary and Conclusions.

The influence of acute epidemic encephalitis on pregnancy, labour and the puerperium is discussed.

(*a*) *On pregnancy* three criteria of influence are separately considered.

(i) *Spontaneous interruption* of pregnancy was not observed in any of the twenty-one cases reported in this review, although two were submitted to Cæsarean section. This is in keeping with previous findings in Great Britain.

On the Continent it is generally held that gestation is liable to spontaneous interruption in a large number of cases.

From a consideration of one hundred and thirty-nine collected cases (not including the author's series) it appears that in the majority pregnancy is wont to proceed to term without mishap; in cases of greater severity interference with pregnancy does occur: in those patients who are still more seriously affected, the issue proves fatal before delivery can take place.

(ii) *Toxæmia of pregnancy.* The facts do not appear to justify the conclusion reached by some authors that pregnant women with this malady are especially prone to toxæmic manifestations.

(iii) *Fœtal death before term* is thought to be common by some Continental writers. Although this contention is not admitted, its occasional occurrence concomitantly with marked encephalitic symptoms is suggestive.

The difference between British and Continental opinion on the question of pregnancy is such that it cannot be ignored. It can be explained on the grounds of a lower British and higher Continental virulence.

It must be admitted that miscarriage or premature labour does occur in some of the most severe cases, this, though not so common as death before delivery, having been reported sufficiently often to make it unlikely that expulsion of the fœtus is a purely incidental happening unconnected with the disease.

(*b* and *c*) *Labour* and the *Puerperium* it is universally agreed are not complicated in any way by the encephalitis, the former only differing in that it is usually painless, the latter in the occasional occurrence of retention of urine which may or may not be due to the encephalitis

The Stage of the Pregnancy, Parity and Their Relations to the Acute Attack.

The present series of cases is of particular value in assessing the effects produced by the stage of the pregnancy at the time of infection and by parity, because on the whole they present a remarkable similarity such as has, so far as I can ascertain, never before been recorded. Although differing, as all cases of epidemic encephalitis do and must differ, in severity, all the women went to term, and gave birth to healthy children, the only exceptions being the two women who were delivered by Cæsarean section; the ultimate outcome in the large majority was the same—Parkinsonism; while in age the correspondence is strikingly close, 13 of the 17 women whose ages were known being in the "twenties." In ascribing an effect to one influence other often equally important factors are apt to be forgotten; at best it is difficult to determine the relative part played by each of the many and various co-existent causes acting in such a condition as epidemic encephalitis during pregnancy. When, however, a group of cases appears in which both the pregnancy and the disease have run a similar course in patients of very much the same age it becomes possible more accurately to estimate the influence of such factors as parity and the stage of gestation. Their assessment founded on such a series as that at present under consideration must be of definite value whether the conclusions be positive or negative.

Regarding the stage reached by the pregnancy at the time of the acute attack the cases are made up as follows:—

Acute attack in the first month of pregnancy.	1
Second	1
Third	4
Fourth	3
Fifth	4
Sixth	1
Seventh	1
Eighth	2
Ninth	3
During the puerperium ...	0
Total	20

(Case 21 is excluded because the acute attack did not take place during pregnancy).

Case.	Age.	Parity.	Stage of Pregnancy.	Result to Mother.	Result to Child.
1. Hall	49	M.	Probably in the early months.	Parkinsonism during the puerperium.	Healthy
2. ,,	24	Pr.	4th month.	Parkm. 3 months after confinement.	Healthy.
3. ,,	32	Pr.	1st month.	Gradually passed into Parkm.	Healthy.
4. ,,	?	M.	? 9th month.	,, ,,	? Cong. epidemic encephalitis (Cæs section).
5. ,,	20	2nd.	3rd month	,, ,,	Healthy.
6. ,,	?	Pr.	3rd month.	Parkm. began from confinement.	Healthy (died when 2 years old).
7. ,,	25	Pr.	3rd month.	Gradual Parkm.	Healthy.
8. ,,	37	10th	6th month.	?	Healthy.
9. ,,	24	Pr.	Last week of pregnancy.	Parkm.	Healthy.
10. ,,	25	Pr.	8th month.	Parkm.	Healthy.
11. ,,	23	Pr.	5th month.	Parkm.	Healthy (till death from scalds).
12. ,,	27	2nd	5th month.	Parkm.	Healthy.
13. ,,	27	3rd	8th month.	Complete recovery	Healthy.
14. ,,	23	Pr.	7th month.	Parkm	Healthy.
15. ,,	?	4th	9th month.	Parkm.	Healthy.
16. ,,	21	Pr.	5th month.	Parkm.	Healthy.
17. ,,	23	Pr.	3rd month.	Parkm.	Healthy.
18. ,,	25	Pr.	4th month.	Recovery.	Healthy.
19. Berkeley & Cockayne	26	5th	5th month.	Parkm.	Healthy.
20. Bonney	30	4th	5th month.	Recovery.	Healthy.

On the whole there is a fairly even distribution between the nine months; it is noticeable that there is no puerperal case in this series, but no importance need be attached to this observation though onset in the puerperium has frequently been described. It can be seen that of the 20 cases 13 were afflicted before and seven after the fifth month; infection then, seems to have been slightly more common in the earlier than in the later stages of gestation. The preponderance, however, though marked, is not of great magnitude especially when considered in conjunction with the smallness of the total number. It is fair to conclude that infection among these pregnant women occurred

independently of the stage of pregnancy at the time they became infected; neither was there any noticeable difference in the course either of the encephalitis or of the pregnancy attributable to this factor. The acute attack in those who were invaded during the early months presented the same features as in those in whom infection did not take place until later; the outcome of that acute attack shows a similar correspondence, most of the cases passing eventually into the Parkinsonian state. Pregnancy in all the women, with the exception of the two who were delivered by Cæsarean section, proceeded to term and healthy children were born.

Further analysis with regard to parity shows that the cases were composed:—

First pregnancy, 11. (Cases 2, 3, 6, 7, 9, 10, 11, 14, 16, 17, 18).
Second pregnancy. 2. (Cases 5 & 12).
Third pregnancy. 1. (Case 13).
Fourth pregnancy. 2. (Cases 15 & 20).
Fifth pregnancy. 1. (Case 19).
Tenth pregnancy. 1. (Case 8).
Multiparæ, in whom the number of previous pregnancies is unknown. 2. (Cases 1 & 4).

Eleven women were attacked during a first pregnancy and eight during subsequent gestations. On the whole, then, an attack is slightly more common in those who are pregnant for the first time. Apart from this, the remarks made about the effect of the stage of the pregnancy appear to apply with equal force to parity; while one woman was attacked when carrying her tenth child, others were pregnant for the first, second or third time. No difference in severity or result is observable which could justly be ascribed to a woman being in this or that pregnancy at the time of infection. The patient (case 8) who was pregnant for the tenth time when attacked was certainly very seriously afflicted; but the severity can hardly be attributed to her multiparity in so much as equally marked features were exhibited by three of the primigravidæ, to wit, cases 3, 10 and 16; not only this, for in one case pregnant for the fifth time the acute attack passed without notice (case 19), while case 12 in her second pregnancy belongs to the mild group, her symptoms not being sufficiently marked to cause her to take to her bed.

On these two questions most authors observe a discreet silence, only a few venturing an opinion. Di Francesco, while unwilling

to make any assertions on the possible influence of attack early or late in gestation, concludes that the outlook in the case of multiparous women is worse than in that of primigravidæ. The ten cases upon which this statement is based he analyses thus:

4 Primigravidæ,	2 deaths.	2 recoveries.
2 Secundiparæ,	1 death.	1 recovery.
4 Multiparæ,	4 deaths.	

He considers the question of age and decides that the greater mortality among the multiparous women was due to their more mature years. He finds confirmation in Bertoloni's figures, for out of 10 women between 20 and 30 he had five fatalities, while out of eight between 31 and 40 he had six deaths.

Now Bertoloni's[12] analysis on this question of parity covered more than the cases mentioned by di Francesco;[39] actually there were 37 cases, 20 of whom were pregnant for the first time; of those 20, 10 died, a mortality of exactly 50 per cent. Of the 17 multiparæ nine died, representing a mortality of almost 53 per cent. The difference is too trifling to be of significance. Moreover di Francesco's[39] argument is in direct antagonism with the findings of Hall and Yates[50] who, in reviewing a large series without special relation to pregnancy, noticed an increase in the number of severe cases in females in the lower age periods. Furthermore, the cases referred to in the previous paragraph will be found fairly evenly distributed with regard to this point. The patient aged 37 (case 8) suffered severely, but, on the other hand, the first case was one of a woman aged 49 in whom the acute attack altogether escaped notice. There is an obvious fallacy in comparing too closely the Italian with the British cases and it may be that the virus in Milan possessed a special predilection for older females.

Parsons,[83] writing on the question in 1922, found that the majority of the 50 Ministry of Health cases occurred among women in whom labour was imminent, in progress or but recently completed. On referring to the details of the cases it has been found that in 20 the disease made its appearance during the seventh, eighth or ninth months, in nine during the third, fourth, fifth or sixth months, and in the remaining 11 after confinement or miscarriage; but in seven of the latter onset was delayed so long that the preceding pregnancy was a more or less remote antecedent whose aetiological significance must be regarded with a certain suspicion. Be this as it may, there can be no doubt that an onset during the later months was more common in those 50 cases.

These cases may be summarized :—

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At or before 6th month.—
9 Cases—6 died.
2 recovered.
1 recovered with sequelæ.
Mortality 66 per cent.

After 6th month.—
20 Cases—5 died.
10 recovered.
5 recovered with sequelæ.
Mortality 25 per cent.

After delivery.—
11 Cases—6 died.
5 recovered.
Mortality 54 per cent.

There can be no doubt that Parsons[83] was on sure ground in making his assertion, for even if the seven cases in which the confinement or miscarriage was a rather remote antecedent be excluded it is seen that whereas nine became infected early in pregnancy, 24 exhibited clinical signs for the first time a little to the one or other side of full time. It further appears that the mortality among those attacked early in gestation is rather heavy.

Bertoloni[12] is in agreement upon the enhanced susceptibility in the neighbourhood of term. He quotes 44 cases in which infection occurred :

from the first to the fifth month	8
during the sixth month	9
during the seventh & eighth months ...	8
during the ninth month	19
	44

or

at or before the sixth month	17
after the sixth month	27
	44

Fort[37] is in general agreement, believing that susceptibility to the disease is increased at about the time of the confinement.

In order to see how far these facts can be said to be true it has been thought advisable to collect a number of cases from the literature. 171 have been found and are briefly analysed as follows:—

Cases infected at or before the sixth month of pregnancy.

Case.	Age.	Parity	Stage of Gestation 3rd.	4th.	5th.	6th.	Result to Mother.	Result to Child.
Ministry of Health.[76] (9)	24.		x				Died.	Abortion before death of mother.
	24.			x			Died.	Not delivered.
	30.				x		Died.	Not delivered.
	26.				x		Died.	Not delivered.
	31.					x	Died.	Not delivered.
	32.					x	Recovered.	Induced.
	30.					x	Recovered with sequelæ.	
	25.					x	Died.	Not delivered.
	35.					x	Recovered.	?
Neal.[79]	25.				x		Recovered.	Healthy and at term.
Bassoe.[10]	34.	8th				x	Died.	Not delivered.
Pansera.[82]					x		Died.	Not delivered.
Valente & David.[57]	34.					x	Recovered.	Healthy and at term.
Poligone[88] (2).	24.	Pr.*			x		Recovered with sequelæ.	Healthy.
	35.		x				Died.	Not delivered.
Audrey & Froment.[6]	30.				x		Died.	Not delivered.
Gaujoux & Vincent.[114]					x		Recovered.	Healthy.
Robinson.[95]	21.	Pr.				x	Recovered.	Healthy (to 9½ months after birth).
		Pr.	x				Died.	Not delivered.
di Francesco.[39]	39.	7th				x	Died.	Dead child delivered by Cæs. sect. after death.
	36.	7th	x				Died.	Extra uterine gestation.
	21.	Pr.				x	Died.	Not delivered.
	20.	Pr.			x		Improved and discharged.	?
	26.	3rd			x		Died.	Not delivered.
Marinesco.[68]	32.	Pr.			x		Died.	Not delivered.
Achard.[1]	25.	Pr.				x	Died.	Miscarriage after fœtal death.
Voron & Pigeaud.[117]	21.	Pr.	x				Recovered.	,, ,,
	19.	Pr.				x	Recovered.	,, ,,
Price.[90]			Early in gestation.				Recovered with sequelæ.	Healthy Cæs. section.
Chauffard.[23]	24.	Pr.		x			Died.	Not delivered.

*Primipara.

Case.	Age.	Parity.	Stage of Gestation 3rd.	4th.	5th.	6th.	Result to Mother.	Result to Child.
Valloix.[37]		Pr.*			x		Died.	Not delivered—attempted induction.
Kreiss.[60]	21.	Pr		x			Recovered.	Induction.
Bompiani.[16]	Young.	Pr.			x		Recovered with sequelæ.	Miniature Cæs. section.
Rossi.[96]				x			Recovered.	Healthy and term.
						x	Recovered.	Miscarriage at 7th month.
						x	Died.	Not delivered.
Benthin.[11]						x	Recovered with sequelæ.	Stillborn.
Bertoloni.[12]	26.					x	,, ,,	,, induction.
	28.				x		Recovered.	Healthy (to 2 years later).
Benthin.[11]	24.					x	Recovered.	Healthy.
Bacialli & Scaglione.[7]						x	Recovered.	Healthy.
Amreich.[2]						x	Died.	Dead and premature vaginal Cæs. sect.
Patek.[84]	27.	Pr.		x			Recovered.	Healthy.
Bompiani.[15]	Young	Pr.	Early months.				Recovered with sequelæ.	Healthy.
Fort.[37]	24.	Pr.	Early months.				,, ,, During subsequent pregnancy.	Miscarriage.
	29.	4th	x				Recovered.	Healthy, at term.
Bué.[19]	41.	Pr.				x	Recovered.	Healthy, at term.
Carnot.[20]	20.	Pr.			x		Died.	Not delivered.
Deoraigne.[30]		Pr.	x				Died.	,, ,,
		Pr.	x				Died.	,, ,,
Euzière & Carrieu.[33]	22.	Pr.		x			Recovered.	Not traced but fœtal heart heard after mother's recovery.
Lereboullet.[64]	22.	Pr.		x			Recovered.	Macerated fœtus.
Marinesco.[68]					x		Recovered.	Healthy.
Roume.[97]	23.	Pr.			x		Died.	Not delivered.
Vidal & Couvelaire.[37]						x	Slow recovery.	Healthy.
Vincent & Gaujoux.[114]	17.	Pr.			x		Recovered.	Healthy.
Dimitz.[31]			Early months.				Died.	Not delivered.
Netter.[80]	28.		x				Died.	Not delivered.

*Primipara.

Cases in which onset occurred after the sixth month but *before the onset of labour.*

Case.	Age.	Parity.	Stage of Gestation. 7th.	8th.	9th.	Almost at term.	Result to Mother.	Result to Child.
Ministry of Health (20)[76]	28.					x	Recovered.	Signs of ep. enceph.
	25.					x	Died.	Signs of cong. syph.
	28.					x	Died.	Healthy.
	33.			x			Slowly recovering.	Died 10 days old.
	35.		x				Recovered with sequelæ.	Premature labour at 7½ months.
	17.			x			,, ,,	Died at 2 days old.
	28.					x	Recovered.	Healthy.
	37.			x			Died.	Not. deliv.
	38.					x	Died.	? ,,
			x				Recovered with sequelæ.	?
	28.					x	,, ,,	Died of ? ep. encep.
	26.					x	Recovered.	?
	31.			x			Died.	Not deliv.
	35.			x			Recovered.	Signs of ep. encep.
Ministry of Health.[76]	40.					x	Recovered.	Healthy.
	27.			x			Recovered.	Healthy.
	25.					x	Recovered.	Stillborn.
	35.					x	Recovered.	Healthy.
	46.		x				Recovered.	?
	40.			x			Recovered.	Stillborn.
Klippel & Baruk.[59]	28.	Pr.*			x		Recovered with sequelæ.	? signs of ep. encep.
Hofer.[56]		2nd		x			Recovered.	Died 2 days after birth (Cæs. section).
Foulkod.[38]			x				Died.	Died at birth
			x				Died.	Healthy (induction).
Gaujoux & Bertrou.[41]	28.	Pr.			x		Died.	Stillborn.
Marinesco.[68]	31.		x				Died.	Died after a few hours. Cæs. sect.).

*Primipara.

Case.	Age.	Parity.	Stage of Gestation. 7th.	8th.	9th.	Almost at term.	Result to Mother.	Result to Child.
Jorge.[57]	30.					x	Recovered.	Signs of ep. enceph.
Schulze.[103]	35.	2nd.	One month post mature				Recovered and died of pul-embolus.	Healthy.
Répond and Werra.[94]	42.			x			Died.	Not. delivered.
Pansera.[82]				x			Died.	Induction & stillborn.
Tiago d'Almeida.[57]	28.		x				Died.	Stillborn.
Novaes & Sousa.[81]	30.					x	Died.	Signs of ep. enceph.
Pimenta.[85]	32.					x	Died.	Stillborn.
Santi.[100]				x			Died.	Healthy, induction.
Mercier, Andrieux &				x			Recovered.	Died ? ep. encp.
Mlle. Bonnaud.[73]	28.	Pr.*		x			Died.	Signs of ep. encp.
Strecker & Willey.[107]	30.					x	Recovered, Parkm. with subsequent pregnancy.	Healthy.
Forget.[36]	22.	Pr.	x				Recovered with sequelæ.	Healthy.
Banister.[8]	31.	Pr.			x		Died.	Healthy, induction.
Price.[90]			x				Died.	Not delivered.
Poligone.[88]	24.	3rd				x	Died.	Delivered dead by post mortem Cæs. sect.
Andérodias[3]	25.	Pr.		x			Died.	Healthy.
Commandeur & Eparvier.[24]	16.	Pr.		x			Died.	Lived 18 hours.
Gaujoux & Flaissier.[42]	23.	Pr.		x			Recovered.	Healthy.
Robinson.[95]	30.	Pr.		x			Recovered.	Lived for 26 days.
,,			x				Recovered with sequelæ.	Healthy.
,,		Pr.				x	Recovered.	Healthy.
Haultain.[51]		Pr.				x	Recovered.	Healthy.
Kreiss.[60]	24.	2nd	x				Recovered.	Died 1 hour after Cæs. sect.

*Primipara.

Case.	Age.	Parity.	Stage of Gestation. 7th.	8th.	9th.	Almost at term	Result to Mother.	Result to Child.
di Francesco.[39]	34.	5th			x		Died.	Healthy.
,,	34.	7th	x				Died.	Dead & premature.
,,	20.	Pr.*	x				Died.	Dead & delivered by post-mortem Cæs. sect.
,,	20.	Pr.	x				Recovered.	Healthy.
,,	33.	9th		x			Recovered.	Healthy,.
Fino & Fubini.[35]	29.	2nd		x			Recovered.	Healthy, induction.
,,	31.	Pr.	x				Recovered.	Healthy. induction.
Benthin.[11]				x			Died.	Dead pre-mature—Vaginal Cæs. sect.
,,	26.	3rd				x	Recovered.	Healthy.
Herd.[55]	24.	Pr.			x		Died.	Healthy.
,,	28	Pr.			x		Recovered with sequelæ.	Stillborn.
Garnett & Washington.[40]	26.	2nd		x			Recovered.	Healthy.
Benthin.[11]	24.	Pr.		x			Recovered.	Healthy.
Bacialli & Scaglione.[7]				x			Died.	Healthy at birth, died 3 days later.
,,			x				Died.	Healthy, died 6 days later.
,,					x		Recovered.	Healthy.
,,					x		Died.	Died 3 days after birth.
Amreich.[2]					x		Recovered.	Healthy.
Waldstein.[118]						x	Died.	Not delivered.
,,					x		Recovered.	Healthy.
Latzko.[62]					x		Recovered.	Healthy. Cæs. section.
Putnam.[91]	26.	3rd		Near term.			Died.	Stillborn.
Turenne.[112]		5th	x				Died.	?
Fino & Fubini.[35]	23.	Pr.			x		Recovered.	Healthy.
Fort.[37]	29.	Pr.	x				Recovered.	Healthy.
,,			Later months.				Recovered with sequelæ.	Healthy.
,,		2 days before confinement.					,, ,,	Healthy.
Brindeau.[37]	30.	Pr.		x			Recovered.	Died 6 weeks after birth at term.

*Primipara.

Case.	Age.	Parity.	Stage of Gestation. 7th.	8th.	9th.	Almost at term.	Result to Mother.	Result to Child.
Cathala.[37]						x	Recovered.	Healthy.
Dèmelin.[37]			x				Recovered with sequelæ.	Healthy.
,,	Young.					x	Recovered.	Healthy.
Euzière & Carrieu.[33]			x				Recovered.	Healthy.
Lasseigne.[37]				x			Recovered.	Healthy.
Marinesco.[68]				x			Recovered.	Healthy.
Millian.[37]		Pr.*	x				Died.	Not delivered.
Netter.[80]	33.			x			Died.	Not delivered.
Valloix.[37]			x				Died.	Premature macerated fœtus.
Dimitz.[31]			Later months.				Recovered.	Healthy.
,,				,,			Recovered.	Healthy—induction.
Kreiss.[60]						x	Recovered.	Healthy—Cæs. sect.
Rèpond.[94]						x	Died.	? Healthy.
Valente & Maraes David.[57]			x				Recovered.	Healthy.

*Primipara.

Cases in which onset has occurred after delivery.

Case.	Age.	Parity.	Time of Attack.	Result to Mother.	Result to Child.
Ministry of Health,[76] (11).	29.		4th day of puerperium.	Died.	Healthy.
	18.		2nd day of puerperium.	Recovered.	Healthy.
	31.		1st month of ,,	Recovered.	Healthy.
	27.		2 days after miscarriage.	Died.	
	32.		4 weeks after confinement.	Died.	Healthy.
	27.		1 month after ,,	Recovered.	Healthy.
	39.		Miscarriage 1 month before	Died.	
	37.		15th day of puerperium.	Died.	Healthy.
	32.		17th day of ,	Recovered.	Healthy.
	40.		1st day of convalescence from Cæs. sect.	Recovered.	Healthy.
	28.		1st day of puerperium.	Died.	Signs of epidemic encephalitis & died 6 days after birth.
Strecker & Willey.[107]	38.		3 weeks after confinement.	Recovered with sequelæ.	Healthy.
,,	32.		1 month after confinement.	,,	Healthy.
Couvalaire & Trillat.[26]	18.	Pr.	2nd day of puerperium.	Died.	Healthy.
Hallé.[47]		Pr.	4th month of puerperium.	Recovered.	Died of ep. enceph.
d'Andrea[4]	40.	7th	2nd day of ,,	Recovered with sequelæ.	Healthy.
Martin, Dechaume[70] & Mallartre.	24.	Pr.	3rd day of ,,	Died.	Healthy.
Robinson.[95]		2nd	1st day of puerperium.	Recovered.	Healthy.
Henneberg.[54]	33.	3rd	During the ,,	Recovered, Parkism. with subsequent pregnancy.	Healthy.
Voron, Dechaume & Mallartre.[116]	24.	Pr.	40 hrs. after confinement.	Died.	Healthy.
Bompiani.[16]	44.	11th	While suckling a baby.	Recovered but Parkm. with subsequent pregnancy.	Healthy.
Fort[37]	24.	Pr.	24 hrs. after confinement.	Recovered.	Healthy at birth died at 12 mths. T.B. glands.

Further analysis shows that,

Of the 58 attacked during the first half of gestation—

27 died.
21 recovered.
10 recovered with sequelæ.
Mortality 46 per cent.

Of the 91 attacked during the second half of gestation—

36 died.
41 recovered.
13 recovered with sequelæ.
1 recovered to die later from pulmonary embolism.
Mortality nearly 39 per cent.

Of the 22 attacked after delivery—

9 died.
8 recovered.
5 recovered with sequelæ.
Mortality nearly 41 per cent.

When viewed in the light of these 171 cases it certainly seems that the conclusion reached by Parsons[83] can be upheld, namely that the attack is definitely more common during the second half of gestation and in the puerperium than during the earlier months of pregnancy in the ratio of 113 : 58 which is roughly equivalent to 2 : 1. Out of three cases, therefore, two may be expected to occur during the later months or early in the puerperium. The mortality figures are not very convincing but suggest a slightly increased death rate when infection takes place early in gestation.

The question now arises whether the course is the same in cases of early and late infection. As regards the encephalitis this question has already been answered by stating that the mortality is slightly higher among those which become infected during the first half of gestation. As regards the pregnancy the answer depends primarily upon the severity of the infection. In cases which are destined to recover there is no apparent difference in the two groups. Fatal cases take one of three courses, some patients die before delivery, others succumb after miscarriage or premature labour, yet others die after confinement at term. The last group is composed mainly of patients in whom the acute attack was delayed until the later weeks.

On analysing the cases in which the fate of the products of conception as well as the date of infection is known it appears that :

of 24 fatal cases infected before the sixth month—
22 died without being delivered... ... 92 per cent.
2 miscarried and died afterwards ... 8 per cent.

whereas of 29 fatal cases infected after the sixth month—
8 died without being delivered ... ... 28 per cent.
10 died after premature labour ... ... 34 per cent.
11 died after confinement at term ... 38 per cent.

It is, therefore, evident that miscarriage during the early months is rare, whereas premature labour later in gestation is relatively common.

Since early infection appears to be associated with a rather higher mortality the general statement made in a previous section upon the course the illness in cases of great severity is confirmed. The most severe cases die before delivery can be accomplished, the least severe go to term and in the intermediate group labour is premature.

It is unfortunate that the records of the parity are very incomplete, reference being made to this point in only 71 cases. These can be grouped :—

Infected at or before the sixth month—
of 29 there were
24 primigravidæ of whom 10 succumbed—Mortality 42 per cent.
five multiparæ of whom four succumbed— Mortality 80 ,,

Infected after the sixth month—
of 33 there were
21 primigravidæ of whom eight succumbed—
Mortality 38 ,,
12 multiparæ of whom five succumbed— Mortality 42 ,,

Infected after confinement or miscarriage—
Of nine there were
five primigravidæ of whom three succumbed—
Mortality 60 per cent.
four multiparæ, all of whom recovered.

Of the 71 :
50 were primigravidæ of whom 21 died— Mortality 42 per cent.
21 were multiparæ of whom 10 died— Mortality 47 ,,

The outstanding fact is the increased susceptibility to infection on the part of those who are in their first pregnancy, primigravidæ being attacked with about double the frequency of multiparæ. This is in keeping with the findings of Bertoloni[12] in whose series of 37 pregnant women, 20 were primigravidæ, and of Tropl[111] who in reporting seven cases noticed that in six the patients had not previously had children. This state of affairs is, after all, to be expected because of the admitted total relative increase in female cases at the lower age periods. There is little else of real value in the above analysis; it would be rash to theorize on such questions as enhanced mortality among multiparous women infected before the sixth month, or lowered death rate in the same class when infection occurred after delivery, because the total number of cases in these groups is only six and four respectively. The fact that the average total mortality differs but little in the two groups goes to show that, on the whole, parity does not exert any marked effect upon the course of the disease.

Conclusions.

(1) The smaller group of 20 patients in whom the acute attack occurred during pregnancy, shows that neither the age of the pregnancy nor the parity of the patients exert any effects upon the course of acute epidemic encephalitis. There is no evidence deduceable from these cases to show that the outcome of the disease differs on account of either of these two factors.

(2) There is, however, a suggestion of increased susceptibility on the part of those in a first pregnancy, 11 primigravidæ having been attacked to seven multiparous women.

(3) The general group comprising 171 cases indicates that infection has been noted more commonly during the later months of pregnancy and after labour is over than in the first half of gestation; thereby upholding Parson's[83] contention enunciated in 1922. This group suggests that the mortality is greater when infection takes place early in pregnancy.

(4) Miscarriage following infection during the early months is shown to be uncommon; severe cases in this group succumbed before delivery. When, however, infection takes place later in pregnancy premature labour is as common as death "enceinte."

(5) The 71 cases in which there is knowledge of the parity suggest that primigravidæ are more frequently attacked than those who have previously born children. Because young females are known to be more prone to infection than women of mature years

it is probable that this enhanced susceptibility among those pregnant for the first time is due to general causes and not specially related to pregnancy, primigravidæ being, on the whole, younger than multiparous women. There is but slight evidence in support of di Francesco's belief that pluriparity makes the prognosis more grave because of increased age. The figures adduced show that the mortality is only slightly higher in the multiparous group.

(6) The 20 cases, which were infected during pregnancy, though differing in some respects, support the general argument that infection is particularly common in young women most of them being in the third decade of life. They neither add to nor subtract from the suggestion that attack early in gestation enhances the mortality, because none of them proved fatal and their clinical course was very similar. They are at variance with the conclusion that infection is more common during the later months in that while these 20 cases were fairly evenly distributed throughout pregnancy as a whole a slightly larger number was attacked during the first half of gestation.

The Child.

Although epidemic encephalitis is not a highly contagious disease, instances of direct infection are not unknown. Occasional infection of a newly born infant from its mother is, therefore, to be expected and has in fact been reported from time to time. Such infection has been variously ascribed to transplacental passage of the virus, to the mother's milk and to other maternal excretions with which the baby comes in contact. Jorge[57] recognizes two distinct types of infantile encephalitis, congenital in which the fœtus becomes infected *in utero*, and hereditary in which infection from one or another maternal source takes place after birth. There has been much argument as to the possibility of the various methods of infection, and differences in opinion are even now rife. It is, however, generally agreed that while infantile infection is possible it is an uncommon phenomenon. The opposite proposition, that children born to encephalitic mothers are endowed with a natural immunity to the disease, has never been enunciated.

On the score of encephalitis epidemica neonatorum the present series of 21 cases is helpful only in that it lends weight to the orthodox view that infection before birth or in early infancy is unusual. In none of the cases is there anything suggestive of infection *in utero;* in one only is there the very faint possibility of infection some time after birth; many of the infants were suckled without incurring harm; in one case (12) the child remained healthy despite

its being subjected to a continuous stream of maternal, and presumably infected, saliva. The children have been traced for varying periods to as long as nearly five years in Berkeley and Cockayne's case (19) and all have remained healthy with three exceptions. Of these, one (Case 11) was born in a mother with Parkinsonian symptoms two years after the acute attack which had occurred during the course of a previous pregnancy; that infant died at the age of six months as the result of scalds. The second exception was Case 6 in which the child died after two years of life from an unknown cause; the third (Case 4) being of special interest, Hall's own words will be quoted: "In one of the earlier cases in which Cæsarean section was performed, the child was taken away from the mother at once and kept apart from her for several months. Curiously enough this is the only case of the series in which anything suggestive of infection has been reported. The mother developed Parkinsonism. The child was in every way healthy until two years of age. She then suddenly lost the use of the left arm. This apparently recovered, but about a month later she lost the use of the left leg. When I saw her in December, 1922, there was some weakness and clumsiness in the left leg suggesting the slight remains of a 'Poliomyelitis.'" He has seen the child again recently and communicated further in the following terms: . . . "there is no doubt that it had an attack of ordinary acute poliomyelitis, which has left behind some weakness in one limb, otherwise it is normal."

These cases show that the child's chances are good, as 100 per cent. of the 20 infants were delivered alive after an acute maternal attack during pregnancy (the case in which the acute attack did not take place during pregnancy being excluded); with one exception they all remained healthy for a sufficient length of time legitimately to discount any untoward influence on them as a result of the mother's disease.

In broad terms the same facts have been observed by other authors, the child's outlook being generally regarded as fairly good provided the pregnancy goes to term.

Certain other aspects of which no hint is obtained from a study confined to these few cases emerge when a wider field is surveyed. Return will be made, therefore, to the 171 collected cases to which reference has already been made in another section of this review.

It will be remembered that in 58 cases the mothers were infected at or before the sixth month of gestation. Of these, 31 lived and 27 died; of the 27 none gave birth to living children, the fates of whom may be expressed as follows:—

Of the 27 dead mothers :

22 were never delivered.
1 was delivered of a 28th week baby, one hour after her own death, by Cæsarean section.
1 fœtus was delivered prematurely by vaginal Cæsarean section.
1 fœtus died before the mother miscarried.
1 mother miscarried and died subsequently.
1 gestation was tubal.

27

There is little need for comment upon these cases; in this group it is obvious that the chance of obtaining a living child is infinitesimally small, the only hope being that the mother's death may be delayed until after viability of the child. It is noticeable that the fœtal mortality appears to be secondary; were it primary, miscarriage would surely be more frequent; in only one case was there evidence of fœtal death before that of the mother. The hope which prompted di Francesco[39] to perform post-mortem Cæsarean section must indeed have been forlorn since gestation had only reached the twenty-eighth week at the time of the mother's death, and it must be admitted that a large number of infants delivered between the twenty-eighth and thirty-second weeks succumb.

Of the 31 surviving mothers who were infected at or before the sixth month :

16 gave birth to healthy infants at term.
1 was successfully delivered, by Cæsarean section, of a healthy infant.
3 fœtuses died *in utero* before the mother miscarried.
2 mothers miscarried and survived. Whether fœtal death preceded or followed the miscarriage is not known.
5 fœtuses were delivered before viability by induction of premature labour or by Cæsarean section.
4 the fate of fœtus is unknown.

31

It is thus evident that the 31 pregnancies resulted in the production of 17 healthy babies, which makes the fœtus's chance of survival to full time equal to almost 55 per cent. But in five cases pregnancy was terminated artficially before viability and presumably, therefore, rightly or wrongly, in the interests of the mother. It is not improbable that some at least of these five would have

proceeded satisfactorily to term had recourse not been had to induction or Cæsarean section. It does not seem unjustifiable to exclude these cases altogether, in addition to those in which the ultimate fate of the embryo is unknown. In one case at least, (Fort[37]), the fœtal heart was heard after recovery of the mother, and it is probable that the pregnancy terminated successfully at term.

In these circumstances, it may be said that of 22 pregnancies in which infection occurred during the early months, 17 terminated in a manner satisfactory to the interests of the child. To the three cases in which the fœtus perished before miscarriage reference will be made later. At this stage it can be asserted that when infection of the mother takes place during the early months of pregnancy the child's outlook varies directly with the prognosis to the mother. It is almost a platitude to say that should she die before the child becomes viable the latter's chances are nil; it is, however, good to know that in the event of her recovery there is a reasonable hope of obtaining a healthy infant at term; this hope corresponds in all probability to a 3 : 1 ratio; or expressed in another way, out of four pregnancies, one will be unfruitful, a figure which shows that the disease, if not fatal to the mother, plays but little part in influencing fœtal mortality.

Passing to a consideration of the 91 cases in which infection was delayed until the second half of pregnancy, the fates of the children of the 37 mothers who died were :—

6 were healthy and born at, or near, term, including one healthy child whose mother died some weeks later from pulmonary embolism.
4 were born dead, but were all premature.
1 was born prematurely and macerated.
3 were born dead at term.
2 showed signs of epidemic encephalitis, but recovered.
8 were not delivered.
4 died a few days after premature birth.
1 died a few days after birth at term.
3 healthy children were delivered artificially either by induction of premature labour or by Cæsarean section.
2 were delivered by Cæsarean section after death of the mother between the 28th and 30th weeks; neither survived.
1 showed signs of congenital syphilis.
2 the fate is unknown or uncertain.

37

In all, 11 healthy children were obtained, naturally or artificially, a combined fœtal and infantile mortality of 70 per cent. in order to eliminate any possibility of argument about the syphilitic case it is better that it be excluded together with the two cases in which the fate of the infant is unknown, reducing the total to 34 cases. It may then be said that the infant's chance in this group is about 32 per cent. and the fœtal and infantile mortality 68 per cent.

The magnitude of this figure is not surprising when investigation is made as to the cause of the mortality. In the first place, the fact that eight mothers died while still carrying their young must not be allowed to escape observation; in the second, it is noteworthy that out of 15 infants who were either born dead or succumbed within the first few days of life no less than 11 were premature. It may be alleged, possibly with some justification, that this "whittling" of the mortality merely begs the question. Not at all. The child's outlook must, of course, be grave in this group which includes cases as early as the twenty-eighth week of gestation. An infant whose mother dies so soon after viability cannot be expected to have much hope of life; the nearer the mother is to term at the time of death the greater are the chances of the fœtus—again a platitude, but a necessary statement in that it proves that the infantile mortality is in large part due to prematurity. Is the prematurity due to the disease? An attempt to answer this question has been made in another place when it appeared that premature labour in the more severe Continental cases is a happening of no great rarity.

Of the 54 mothers who were infected after the sixth month and survived:

30 healthy infants were born at term.
3 healthy infants were delivered successfully after induction of premature labour.
4 infants exhibited signs of epidemic encephalitis and recovered.
2 infants exhibited signs of epidemic encephalitis and died.
2 healthy infants were delivered by Cæsarean section.
2 premature infants died shortly after delivery by Cæsarean section.
3 premature infants succumbed within a few hours or days of birth.
4 premature infants were dead at birth.
3 the fate of the infants is unknown.
1 infant, healthy at birth, died from unknown cause at the age of six weeks.

54

Thus 39 infants, excluding the child which was healthy at birth but died six weeks later from unknown cause, survived out of a total of fifty-five; excluding from that total the three whose fates are unknown, and the one which died from unknown cause, that number becomes reduced to 50, making the infantile mortality 22 per cent. A glance at the table will show that the mortality in this group, as in the former, is due in the large majority of cases to the prematurity rather than to the disease; for out of the 11 children who died in only two has it been suggested that death was due to encephalitis, and of these two, in one only was the diagnosis confirmed post-mortem (Santi's second case[100]).

Out of 22 mothers infected during the puerperium, 13 lived and 9 died. The fates of the children of the nine mothers who died were :

6	remained healthy.
1	showed signs of epidemic encephalitis and died.
2	fate unknown.
9	

Of seven infants whose fates are known one died, a mortality of 14 per cent. Owing to the smallness of the total number, it is probable that this figure is rather too high.

Of the thirteen mothers infected during the puerperium who lived :

11	children remained healthy.
1	child showed signs of epidemic encephalitis and died.
1	child died from another cause at the age of twelve months.
13	

The mortality in this group is, therefore, about seven per cent.

Maternal infection during the puerperium is thus seen to be associated with a low infantile mortality, a fact which emphasizes the rarity of transmission of the disease from mother to offspring.

Collecting the results obtained in each of the six groups, and excluding cases in which the fate of the child is unknown :—

	Cases.	Surviving infant.	Fœtal and infantile mortality.
GROUP 1.			
Fatal maternal infection before the 6th month	27	0	100 per cent.
GROUP 2.			
Non-fatal maternal infection before the 6th month	27	17	37 ,, ,,
GROUP 3.			
Fatal maternal infection after the 6th month	34	10	68 ,, ,,
GROUP 4.			
Non-fatal maternal infection after the 6th month	50	39	22 ,, ,,
GROUP 5.			
Fatal maternal infection during the puerperium	7	6	14 ,, ,,
GROUP 6.			
Non-fatal maternal infection during the puerperium	13	12	7 ,, ,,
Total in all six groups	158	84	46 per cent.

It would seem, therefore, that more than half the total cases are productive of children who survive for more than a few days, regardless of the stage of the pregnancy at the time of the acute attack, and of the fates of the mothers. This is in keeping with previous findings of which two examples will be quoted, those of Bertoloni[12] and of the Ministry of Health.[76] The former was able to trace 37 children of whom 18 survived for more than a few days or weeks; according to his figures, therefore, the combined fœtal and infantile mortality is equivalent to about 51 per cent. There are 32 relevant cases in the Ministry of Health Report,[76] 15 surviving infants resulting, a mortality of 53 per cent. The close approximation of these three—46, 51, and 53 per cent.—is noteworthy and indicates that the fœtus has about an "even" chance.

This bald statement, however, must be considered in conjunction with the six groups into which the cases have been divided. It is further worthy of remark that the maternal death rate roughly corresponds to the combined infantile and fœtal mortality. This is, of course, to be expected, more particularly in those patients who were in the earlier months of pregnancy at the time of onset of the disease. It is not surprising that Groups 1 and 3 comprising the fatal cases should be associated with fewer live infants than Groups 2 and 4 in which the mothers recovered; these observations lead to the equally to be expected conclusion that the nearer the

pregnancy is to term at the time of the acute attack the greater is the hope of obtaining a surviving baby. Of the cases attacked during pregnancy and in which the disease passes to recovery, about three-quarters of the infants may be expected to live. When the onset in the mother is delayed until the puerperium the child's risk is slight.

The Dead Children.

It becomes apparent, moreover, that in those cases in which the issue as regards the fœtus or infant is unfavourable, the factors contributing to that issue are maternal death before delivery, interruption of the pregnancy before viability, whether natural or artificial, similar interruption after viability but before full time, stillbirth at term, intra-uterine death of the fœtus and infantile epidemic encephalitis.

In order more precisely to determine the importance of each of these causes of death a table is appended which includes the 73 cases fatal to the fœtal or young infant.

MATERNAL INFECTION.

	Before the sixth month.	After the sixth month.	Puerperium.	Total.
Mother died before delivery.	22	7		29
Interruption before viability, natural or artificial.	7			7
Interruption after viability, but before term, natural or artificial.	2	22		24
Intra-uterine fœtal death.	4	3		7
Infantile epidemic encephalitis.		2	2	4
Stillbirth at term.		2		2
Total	35	36	2	73

The predominant causes are clearly the mother's death and prematurity, accounting together for 73 per cent. of cases fatal to the offspring, the former in the earlier months, the latter in the second half of pregnancy.

The Surviving Children.

What can be said of the 85 infants who survived birth for more than a few days or weeks? Unfortunately, not very much, because the majority are lost sight of soon after their mothers' recovery or death; writers content themselves with remarking that the infant

was healthy at birth and remained so until the mother's discharge from hospital; the interval between observation and publication is often short, and further communications are rare. The only definite statement which can be made is that with few exceptions the children remained healthy for as long a period as they were watched. This period varied from several years in some cases (Strecker and Willey[107]) to a few weeks in others. The exceptions have reference to an odd case here and there in which the child fell victim to some extraneous ailment or accident. Writing on this question, Hall (personal communication) says that so far as his own eighteen cases go "the child does not appear to be affected in any way by the acute attack of encephalitis in the mother. I say 'appear to be' because it is impossible to say how far effects may have been produced which will only show themselves at a later stage of development." His opinion, as always, must carry great weight, and it is quite possible that the future may prove his wisdom in thus gently applying the brake. Nevertheless, there is a significant absence from the literature of further reference to the majority of the children, a fact which renders improbable subsequent encephalitis, for cases of that nature would be sure to attract the attention of clinicians .

It must not be allowed to escape notice that many of the collected cases occurred as long as eight or ten years ago and the profession is still awaiting a communication on "delayed infantile infection" or some similar subject. Adding together this negative information, if so it may be called, the few positive facts to be found in the literature and the known fates of the children in the 20 cases reported here in which the acute attack occurred during pregnancy, it does not seem outrageous to assert that if signs of encephalitis do not develop in early infancy there is little likelihood of their subsequent appearance, and that there is nothing to suggest that the children of encephalitic mothers suffer any later mental or bodily infirmity as a result of their unfavourable birth environment.

Encephalitis Epidemica Neonatorum.

The question of infection of newly born infants has aroused widespread interest from the earliest days of the disease when Harris[52] in this country and Novaes and Sousa[81] in Portugal recorded cases in which the infants exhibited symptoms similar to those of their mothers. The possible sources of such infection are :—

(*a*) By passage of the virus across the placenta.
(*b*) From the mother's milk.

(*c*) By contagion from the mother or from some maternal secretion other than milk.

(*d*) From some source not maternal.

The relative merits of each of these possibilities will now be discussed in turn.

(*a*) *Infection of the fœtus in utero.*

The evidence in favour of infection *via* the placenta is pathological and clinical, the former being both histological and experimental.

(i) *Pathological evidence.*

A. *Histological.*

Histological evidence implies the finding of characteristic changes in the brains of unborn fœtuses, of still-born children and of infants dead so soon after birth that infection from any other source can be fairly and reasonably excluded. In this connexion it is important to realize that the criteria must be absolute, the discovery of intra-cranial hæmorrhages cannot be accepted as proof in the absence of the more definite histological changes.

The likelihood of such ecchymoses being due to birth injuries, as in Commandeur and Eparvier's[24] case, is too great to admit them in evidence. Labour being easy and painless in these cases precipitate birth is probably more common than is suspected. If, however, microscopical changes, the most important of which is perivascular cuffing, are discovered, then the case for transplacental passage is proved. Reference in full to Marinesco's[68] and Kononowa's[48] cases will be found in the section of this review devoted to "Pathology;" those authors have established the possibility of infection by this route, while Santi's case,[100] though not quite so conclusive, lends added weight.

B. *Experimental.*

In 1922, Levaditi, Harvier and Nicolau[65] proved experimentally that the virus can cross the placental site. They inoculated pregnant rabbits with virus obtained from human sufferers dead of the disease. These animals succumbed, whereafter positive results were obtained on re-inoculating other rabbits with extracts of brain, placenta, mammary gland and liver from the dead mother rabbits as well as with extracts of the central nervous system of the embryos.

Bacialli and Scaglione[7] had previously, in 1921, failed to transmit the disease to animals by inoculation with maternal blood, fœtal blood, maternal and fœtal cerebro-spinal fluid, and placental

emulsion obtained from two cases in which the mothers died shortly after giving birth to dead premature infants. These results show that transmission across the placenta does not always occur, even in severe cases, a fact which is now well established.

Jorge[57] has described "suggestive changes" in the placenta, comprising areas of degeneration which grated when cut with a scalpel. The suggestion that such are products of the disease cannot be accepted; Jorge's "areas of degeneration" do not differ, in description at all events, from that which is frequently found at the routine examination after completion of the third stage of labour. Many authorities, including Santi,[100] Fort[37] and other staunch advocates of the theory of transplacental passage, refer to the placenta as normal.

(ii) *Clinical evidence.* There are two ways in which clinical as opposed to post-mortem evidence can help in the elucidation of this problem; on the one hand frequent death of the fœtus before term would be suggestive, particularly if such death bore a definite time relation to the onset of encephalitis in the mother, or if it could be shown to be related to the severity of the maternal attack; on the other hand there is the group of cases in which apparently definite signs have been manifested by children who have survived for a sufficient length of time for such signs to have been observed.

A. *Fœtal death before term.*

Fœtal death before term has been definitely reported seven times, Achard,[1] Putnam,[91] Voron and Pigeaud[117] (2), Lereboullet,[64] Valloix,[37] Répond and Werra.[94] Whether it is more frequent than appears is difficult to say, the criteria being uncertain in the earlier weeks of gestation. The mother sometimes dies before giving birth to her dead fœtus, as in Répond's[94] case and evidence of fœtal life is not always obtainable, since the period over which observations can be conducted is often short in the more severe cases; it is just these in which death of the fœtus is most to be expected. There are, however, these seven undoubted cases, five fatal, all severe, in which there is proof positive of fœtal death; the latter appears to occur when the symptoms of epidemic encephalitis become most marked. The time for which the mother carries the dead embryo is variable, in Voron and Pigeaud's[117] first case a three months embryo was expelled at the twenty-fourth week, whereas in Achard's[1] case the fœtal heart sounds had only been absent for 24 hours before the onset of premature labour. On the whole it may be tentatively said that in the most severe cases the fœtus dies and the mother succumbs soon after, without giving

birth; in cases not quite so severe the mother miscarries a few days after fœtal death; while in cases which are going to recover miscarriage may be delayed for a period of weeks or even months.

B. *Clinical manifestations.*

Clinical manifestations have been reported nine times—Ministry of Health[76] (3), Harris,[52] Novaes and Sousa,[81] Klippel and Baruk,[59] Hallé,[47] Santi,[100] and Mercier, Andrieux and Bonnaud.[73] In three of these (Ministry of Health[76] (2), and Novaes and Sousa[81]) signs were present almost from the moment of birth; in the remainder the onset was delayed for from seven to 14 days. Two infants succumbed, one after early, the other after late onset; all were breast fed except in the case of Mercier, Andrieux and Bonnaud,[73] in which the baby was segregated from the mother. In all cases there was a noticeable similarity in signs between each infant and its own mother; when, for instance, myoclonus formed a prominent feature of the maternal attack, the baby was the subject of similar movements. There is no correspondence in severity either in the group as a whole or between individual mothers and children.

It cannot be denied that these cases are open to argument, but taking all things into consideration it does look as if they are genuine examples of encephalitis epidemica neonatorum; because of the brevity of the interval between birth and the appearance of symptoms, coupled with pathological evidence, it is not improbable that the virus obtained access to the nervous system of the fœtus *via* the placenta. This probability is increased when it is remembered that in one case (Mercier[73]) signs appeared in spite of separation of mother and child from birth.

(*b*) *Infection from the mother's milk.*

It has been argued that transplacental infection does not satisfactorily explain cases of infantile encephalitis in which infection is delayed until after the lapse of a few days of apparent health, and the hypothesis of milk infection, has been offered in its stead. In particular Veksin[113] and Klippel and Baruk[59] strongly support this theory; the two latter describe a suggested case in which the infant born at full time and healthy, fell, after two or three days of life, into a condition of torpor in all ways comparable with that of the mother. The child was breast fed until the eighth day, when it was weaned; thereafter improvement was rapid and a good recovery followed. Protagonists of this view draw a parallel between saliva which has been proved to contain the virus and the secretion of the mammary gland; if it is found in one, why not in the

other? The more venturesome have even suggested that there are in these cases definite physical signs in the breasts due to the disease.

When examined critically this theory can be seen to be little more than a mere speculation. It starts with an unfounded assumption, namely, that because clinical manifestations are delayed, therefore, infection could not have been present in the infant's body before birth. The virus of epidemic encephalitis is known to have a habit of lurking in the body without giving rise to definite clinical phenomena, as evidenced by recrudescences in adults. It is not easy in any given case to be certain that a child at birth is free from symptoms which a few days later become marked. And is the healthy interval so very long after all? In Klippel and Baruk's[59] case the brunt of the attack was over by the eighth day, while in none of the others have signs been delayed for more than a few days, with the single exception of Mercier's[73] in which onset did not occur until the second week. But this child was not fed at the breast and was separated from the mother as soon as born: evidence most damning to the theory of milk infection.

It is true that the virus is believed to live in saliva in combination with cells of the buccal epithelium—it has an epitheliotropic affinity, seen to an extreme degree in Guillain, Kudelski and Lieutrand's[45] case which presented a complete von Mikulicz's syndrome; its neurotropic affinity is of course obvious. It is also true that a fair analogy can be drawn between the breast and the parotid salivary glands since both are ectodermal growths, the one inwards from the skin, the others outwards from the stomodeum: the nervous system, too, is of ectodermal origin. But though the epithelium of the mammary and parotid glands is embryologically similar, and though the histological characters are not dissimilar, their secretions differ markedly in composition and function. Because the virus finds congenial surroundings in saliva plus buccal epithelium, it does not follow that a medium composed of milk with lactiferous duct epithelium will be equally advantageous to its livelihood and to the preservation of its pathogenic properties.

The finding of physical changes in the breasts of mothers whose infants have been weaned or never put to the breast need surely be no cause for surprise, inasmuch as the only signs which have been observed are pain, tenderness and firmness to the touch, common manifestations in cases of this nature.

Furthermore, analogy can be answered by analogy. Is disease in general commonly transmitted to offspring through the medium of the mother's milk? The answer to this question is emphati-

cally in the negative. It is well to recall that the streptococcus of scarlet fever has been isolated from cow's milk, yet it is not proven that infection by the mother's milk ever occurs although infants born to scarlatinal mothers are liable to contract that disease. Is Malta fever spread to the baby by human milk infection? Yet the bacillus melitensis has its normal *habitat* in the milk of goats. If authorities on such diseases as these remain unconvinced surely in encephalitis the doubts must be increased a thousand-fold for the virus has never been isolated from the mother's milk nor have any experimental records been traced which show that human milk is ever pathogenic except in cases of breast abscess. True enough, Levaditi, Harvier and Nicolau[65] obtained positive results with an extract from the mammary gland of an artificially infected pregnant rabbit, but that is not good evidence when all the rest is so very slender. This theory of milk infection had best be laid aside until proof more definite is forthcoming.

(*c*) *Infection from maternal secretion other than milk or by contagion from the mother.*

The ordinary mode of contraction and dissemination is shrouded in such mystery that it is difficult to speculate upon the most likely source from which the newborn babe becomes contaminated. There is, however, definite evidence that the virus lingers in the saliva not only of sufferers from the disease but of otherwise healthy carriers. It might, therefore, reasonably be supposed that in some cases infantile infection takes place from the saliva of the mother; indeed such a mode would be expected to be rather common, firstly because of the continuous and uncontrollable salivation which is such a marked feature in some cases, and secondly, because of the maternal habit of kissing. The only evidence which has been found on this point is that furnished by case 12 in which the infant was for eighteen months subjected to such a stream of saliva with no ill effects. This is admittedly an isolated example but, combined with the rarity of infantile infection, it does make it worth while to speculate whether this disease is similar to syphilis in that an infected mother cannot harm her own child after birth?

Of the other possible maternal sources of infection nothing can be said but this, that no one has produced any material upon which to base conclusions. If it be true that the nasal and pharyngeal secretions harbour the virus then these secretions stand on equal ground with those of the salivary glands. Contagion, it cannot be denied, must necessarily be possible; spread in this way is known to occur occasionally in adults. On the other hand, the fact that

Marinesco[68] found post-mortem changes in an undelivered fœtus, together with the case of Novaes and Sousa[81] in which the baby showed myoclonic movements while being born, points in another direction. The answer to this argument is obvious—that both sources of infection are possible and that although infection may sometimes take place before birth, in other cases contagion cannot be excluded.

(*d*) *Infection from some source not maternal.*

The evidence against infection of the newborn from ordinary sources is entirely presumptive; the presumption being that when the disease becomes manifest during early infancy the virus is of maternal origin. Young children are known to be attacked not infrequently, and in those cases in which the mother suffered during her pregnancy it must be extremely difficult to decide whence the infection came. Since, however, contagion has been known to occur in a few adult cases support is lent in a certain measure to the presumption enunciated above. Additional weight is given by the evidence which favours transmission across the placenta and because, speaking broadly, it may be said that whereas epidemic encephalitis in young children is usually of considerable severity, yet in the group of cases under consideration the disease does not on the whole run a particularly serious course. Should a case occur in which clinical phenomena were long delayed the question of what may be termed "ordinary" infection would arise and could not legitimately be excluded. The fact remains that such cases have never been reported up to the present time, in view of which it seems foolish to argue *ex nihilo* against not unreasonable evidence and against clinical instinct.

Finally, it is only fair to add, all modes of infection may be acting each independently in any given case. Because in one the virus enters the fœtal nervous system before birth there is no reason why in another it should not be derived from a different source, and contagion in particular cannot be excluded. It thus becomes necessary to distinguish between congenital and acquired encephalitis of the newborn, both of which may exist. The difficulty lies in their differentiation, which at the present time is quite impossible and purely theoretical.

Summary and Conclusions.

(1) A study of the 20 cases of Hall and Berkeley shows that the infants were all healthy at birth, and that they have remained so with the exception of two who fell victims to accident or disease, other than epidemic encephalitis, some time after birth, and of one who died from unknown cause at the age of two years.

(2) Healthy infants were, therefore, born in 100 per cent. of cases, among whom the survival rate is 85 per cent. The satisfactory level of these figures is probably related to the low maternal death rate in the series.

(3) A general series of 158 collected cases in which the fate of the fœtus is mentioned, is studied with reference to the fœtal and infantile mortality, cases being grouped according to the stage of pregnancy reached at the time of onset of the encephalitis and to the result in the mothers.

(4) On this basis it appears that the combined fœtal and infantile mortality varies directly with the stage of gestation and the maternal issue. The figures being in each of six groups:—

1.	Fatal maternal infection before the sixth month	100 per cent.
2.	Non-fatal ,, ,,	37 ,,
3.	Fatal maternal infection after the sixth month	68 ,,
4.	Non-fatal ,, ,,	22 ,,
5.	Fatal maternal infection during the puerperium	14 ,,
6.	Non-fatal ,, ,,	7 ,,

5. The general combined fœtal and infantile mortality is equivalent to about 46 per cent. a figure in excess by three per cent. of the maternal mortality in this series. This, though not altering the opinion expressed that the prognosis to the child varies directly with that to the mother, shows that fœtus and infant are subjected to slight additional risk.

(6) A study of the 73 cases non-productive of living or surviving children shows that the most common causes of an issue unfavourable to the embryo are maternal death before delivery in the earlier months and prematurity in the later.

(7) The known subsequent good health of the children in the author's series in some cases to as long as five years, and occasional references to similar cases in the literature coupled with an absence of any published communication on such subjects as "delayed infantile infection," suggest that if an infant safely negotiates the first few weeks of life, there is little likelihood of subsequent development of the disease.

(8) Sufficient cases have now been reported to establish "encephalitis epidemica neonatorum" as a definite clinical entity, though rare.

(9) Such cases run a course often mild, sometimes severe. They are not associated with a particularly heavy mortality. Corresponding symptomatically with the disease in the mother they do not correspond in severity.

(10) There is evidence, both pathological and clinical, to show that the virus is capable of making its way across the placenta, and that, therefore, some of the reported cases have become infected before birth.

(11) There is little to substantiate the belief that on occasions infection occurs by way of the mother's milk.

(12) Infection from maternal sources other than milk does not appear very probable. What evidence there is points in another direction. The question has received but passing notice in the literature.

(13) Infection of newly born infants from ordinary sources is against presumption and clinical instinct. Infection many months after birth might well occur in this manner, but has not yet been reported.

(14) In the present state of knowledge it is well to distinguish, theoretically, between congenital and acquired epidemic encephalitis, of the new-born. In the opinion of the writer the existence of the latter is open to doubt.

Diagnosis.

To establish a diagnosis of epidemic encephalitis in the pregnant woman is easy provided the symptoms are not too obscure and that an epidemic is known to be raging at the time. In such conditions diseases due to the pregnancy might be mistaken for encephalitis. The onset and incubation period, followed by a group of changing clinical manifestations, the predominant features of which correspond to those exhibited by known sufferers in the same locality at the same time, do not leave any room for doubt. Difficulties arise because the two conditions relating to severity and occurrence in epidemic form are not always present. Mild cases often escape notice or are diagnosed as influenza apart from any connexion with gestation. Sporadic cases of all grades of severity give rise to many errors, particularly when associated with pregnancy; symptomatically the differences between some cases of encephalitis and such conditions as eclampsia and chorea gravidarum are not great; the latter are present in the mind of the obstetrician, the former absent; confusion is, therefore, not uncommon and is apt to arise in three different groups of cases. Firstly there is the group in which some form of toxæmia is suspected, from mild toxæmic vomiting at one extreme to fully developed eclampsia at the other, while betwixt and between are cases which simulate moderately marked pre-eclamptic toxæmia. Secondly there are those cases of epidemic encephalitis, choreiform

in type, which are frequently dubbed chorea gravidarum. Lastly comes the general group in which a condition due to the pregnancy can be definitely excluded, but in which the encephalitis is mistaken for some other incidental disease including those as diverse as cerebral tumour, scarlet fever and acute appendicitis.

(*a*) *The "Toxæmia of Pregnancy" group.*

Pre-eclamptic toxæmia. One of the most fruitful sources of diagnostic error lies in the difficulty of differentiating between epidemic encephalitis in its earlier stages and pre-eclamptic toxæmia. Consider for a moment the case of a patient whose illness began with nausea, vomiting and headache, and who has since become drowsy and noticed some visual disturbance, flashes of light, diplopia or amblyopia, in the absence of disc changes. Such a clinical picture offers a very difficult problem, the solution of which depends upon a careful weighing of the pros and cons rather than upon any one specific test, clinical or biochemical. The condition of the urine, as in Victor Bonney's case is the most important observation to be made; in marked toxæmia the amount of albumin is considerable, in the majority of cases of encephalitis only slight; there are, unfortunately, exceptional cases (Poligone,[88] Benthin[11]) in which albuminuria is marked and in which the diagnosis is consequently obscured. The quantity of urine secreted is diminished in pre-eclamptic toxæmia; encephalitis is more often associated with retention than with suppression, the later is excessively rare, and when it occurs its appearance is delayed until the later stages of the disease in cases of considerable severity when other signs will have pointed in the right direction. The blood pressure is raised in the pre-eclamptic woman, it is normal in the encephalitic; the former is rarely the subject of fever, the latter may be. Toxæmia of the grade at present under consideration is extremely rare before the sixth month and very much more common in first than subsequent pregnancies; encephalitis is relatively common early in gestation and in multiparæ; actually it occurs with greater frequency in primigravidæ, a fact which necessarily lessens the value of this point. Œdema of hands, eyelids or vulva is a common accompaniment of the more severe degrees of toxæmia and if present greatly favours such a diagnosis. Œdema of the lower limbs, because it may be due to pressure, is clearly of less value. The laboratory tests for renal and hepatic function help to distinguish between the two conditions in that the blood urea and non-protein nitrogen are not raised in epidemic encephalitis, neither is Fouchet's reaction positive. Post-mortem liver and kidney findings in some

cases of this disease are admittedly similar to those in eclampsia, but such cases have usually run a prolonged course and will have exhibited other unmistakable stigmata. There are thus many points of difference and cases in which the symptomatology is so similar that a genuine doubt remains after weighing each single one are rare. There is usually something about the patient with encephalitis which cannot be made to fit a diagnosis of toxæmia, the mistake often arising because the former is not considered. Poligone[88] reported a case diagnosed and at first treated as one of toxæmia. The patient was a woman of 24 in the ninth month of her third pregnancy. She became ill with vomiting, dimness of vision and diplopia; the urine contained much albumin but was of normal quantity. Within a few days the appearance of abdominal and upper limb myoclonus, with typical lethargy and a raised temperature, disclosed the nature of the disease. At the onset the malady had been mistaken for toxæmia of pregnancy on account of the albuminuria, and consecutive eclampsia feared. The mistake can readily be understood, but let it be noticed that the woman had two previous uncomplicated pregnancies to her credit, that she was passing a normal quantity of urine and that her blood pressure was not raised. When all is said, however, it cannot be denied that there are occasional cases the true nature of which remains uncertain; if this be so the indication is to adopt treatment compatible with a diagnosis of pre-eclamptic toxæmia, no great harm will result and a few days of grace will be obtained during which the development of additional signs will settle the question.

Eclampsia. Fully developed eclampsia is sometimes simulated —Benthin,[11] Foulkod,[38] Bompiani,[15] Herd[55] and others. There is a striking resemblance between the case of epidemic encephalitis which begins suddenly with a fit and that of eclampsia in which there are no preliminary warning toxæmic manifestations. Fortunately, for the sake of diagnosis, encephalitis rarely announces its presence in this way, while in the eclamptic there is, more often than not, some previous danger signal.

Cases presenting excito-motor phenomena in association with rather deep lethargy are of the type in which confusion is liable to arise. As in the case of pre-eclamptic toxæmia, the urine is the most important guide, but, because of the occasional occurrence of well marked albuminuria, retention and even anuria in encephalitic patients, that indicator may fail. It was the present of albumin in the urine which led Herd[55] to a wrong diagnosis despite a normal blood urea, a normal quantity of urine and blood pressure very slightly higher than normal (130 mm. Hg. in a primigravida

aet 24). These data are sufficient to throw grave doubt on the diagnosis of eclampsia. The coma in his case seems to have been complete, an unusual feature in encephalitis and one to which great weight would rightly be attached in differentiation. Let it not be forgotten that the woman with epidemic encephalitis, though stuporose and lethargic, is generally capable of being roused by speaking or shouting, and when aroused responds intelligently to questions. It might, not unreasonably, be thought that myoclonic movements were quite unlike the eclamptic fit, which is usually intermittent, beginning with premonitory twitchings of the face, hands or feet, clean cut with its premonitory, tonic and clonic stages; but on occasions one fit may follow so closely on another as to make the resemblance to the myoclonus of epidemic encephalitis complete. Myoclonic spasms may be, rarely it is true, accompanied by complete loss of consciousness in the early stages and, therefore, painless; more characteristically they are painful at commencement and bizarre in distribution, though showing a special predilection for the musculature of the upper half of the anterior abdominal wall. It is the case with myoclonus affecting the muscles of the face which offers the most baffling problem and which caused difficulty to Benthin[11] and Bompiani.[15] The latter, whose patient became afflicted during the first half of pregnancy, was led by a consideration of all the facts to a correct diagnosis; the former wrongly diagnosed eclampsia. Viewing these cases retrospectively it is easy to say that both were associated with a unilateral facial paralysis, that in one (Benthin's[11]) the pupils were unequal, while in the other there was left sided muscular hypotonia, that in neither was the blood pressure noticed to be raised, facts not in keeping with eclampsia.

It would be possible to continue this process and quote many cases in which some sign or signs show, retrospectively, that the diagnosis of eclampsia should not have been made; the armchair critic can easily find some vulnerable point. Nevertheless, the practical difficulties are such that every now and then uncertainty must be allowed to prevail and the patient treated provisionally as an eclamptic.

Hyperemesis Gravidarum.

The difficulty of determining the cause of vomiting during pregnancy is well known and the diagnosis of hyperemesis gravidarum is made largely because of the absence of collateral signs and symptoms which point to "associated" vomiting due to one or another cause. It, therefore, follows that the case of epidemic encephalitis in which the onset, particularly if about the middle of

pregnancy, is marked by vomiting in association, perhaps, with headache and other slight general phenomena, cannot be disinguished from the case of hyperemesis gravidarum. The routine laboratory tests must be made and treatment conducted accordingly. If the diagnosis be between neurotic vomiting of pregnancy and epidemic encephalitis expectant treatment should be adopted and the patient watched for the development of such symptoms, and signs as lethargy, eye signs, insomnia. Vomiting which continues in spite of treatment will necessarily be associated with a raised ammonia coefficient and if, under such conditions, there is still doubt because of a continued absence of definite stigmata, then the uterus should be emptied. The difficulty lies in the fact that the case of encephalitis may progress along lines very similar to the so called gastro-hepatic type of hyperemesis gravidarum, delirium, delirious coma and fever being common to both conditions. The differential diagnosis from the vomiting associated with pregnancy nephritis and eclampsia has already been discussed.

(b) *The "Chorea Gravidarum" group.*

There is a group of cases, exemplified by case 18, in which epidemic encephalitis mimics very closely chorea of pregnancy. In the majority of cases the movements differ in the two conditions both as regards distribution and character, in chorea gravidarum the facial muscles almost never escape while the limb movements are of great violence and fully completed. Encephalitis, on the other hand, often leaves half or the whole face unscathed, as in case 18, while the movements are usually less complete than in chorea. Even so, in some rare cases the movements are identical and the diagnostic difficulties correspondingly great. These are added to by the frequent progress of the advanced excito-motor cases along positive lines; delirium, insomnia, emotional outbursts and a tendency to mania are of common occurrence, all of which signs are highly characteristic of chorea gravidarum. In such cases the diagnosis must be made on the history and certain other points. Chorea gravidarum almost invariably makes its first appearance in primigravidæ at the third or fourth month. Onset later in pregnancy should always rouse suspicion, as in Commandeur and Eparvier's patient[24] who was within a few days of term when she developed what was at first thought to be chorea of pregnancy. Many patients with the latter disease have suffered from chorea as children or have previously had rheumatic fever. Concomitant cardiac lesions make the diagnosis clear, while the presence of subcutaneous nodules at the elbows and wrists suggest a rheumatic and therefore a choreic tendency.

Encephalitis may appear at any time during a first or subsequent pregnancy, there is no previous history of chorea or rheumatic fever in childhood and associated cardiac lesions are absent, the history is usually one of a few days malaise and an interval followed by muscular twitchings and delirium. Questioning either the patient or her friends will often elicit the story that a week or two ago there was a feeling of drowsiness with one or other of the many symptoms of encephalitis at its beginning, and that before this the health had been excellent. Alternatively in cases with sudden myoclonic onset the history is completely negative.

(*c*) *The "General" group.*

To write a complete account of the differential diagnosis between epidemic encephalitis and all the diseases with which it has been confounded is not in keeping with the scope of this article; the subject is admirably dealt with in the textbooks and monographs by those physicians who know the difficulties and pitfalls from a wide practical experience of the disease. Present purposes will be best served by giving but scant attention to this problem, which must always in equivocal cases lie outside the obstetrician's province. It is, however, well to recall some conditions which cause difficulty. In the first place organic disease of the nervous system other than epidemic encephalitis may be suspected; cerebro-spinal syphilis, cerebral tumour and meningitis, particularly tuberculous meningitis, are often difficult to exclude. The Wassermann reaction in blood and cerebro-spinal fluid will eliminate the first named from the list, while the characteristics of the cerebro-spinal fluid are diagnostic in all forms of meningitis save the tuberculous. Fundal changes are commonly present in the better developed cases of tumour, very rarely in encephalitis. In the second place, functional disease of the nervous system may in error be diagnosed. Fino and Fubini[35] draw particular attention to hysteria in the differential diagnosis, pinning their faith to the eye signs which stamp the case as encephalitis; Mattirolo[71] points out the differences between hysterical stupor and lethargy. Thirdly, the possibility of mistaking cases of epidemic encephalitis which begin with painful abdominal myoclonus for acute abdominal conditions must not be overlooked; the mistake is obviously serious and has led to an occasional unnecessary operation. To regard such a case as one of tabes dorsalis with gastric or renal crises is less serious in its consequence though not to be commended on scientific grounds. Fourthly and lastly, there is the error of mistaking the rash of encephalitis for a scarlatinal eruption or the coryza and other catarrhal symptoms at onset for early measles.

Treatment.

Firstly, the epidemic encephalitis must be treated as such on orthodox lines. Briefly this implies rest in bed with a diet suitable to a febile disease often associated with anorexia, the treatment of symptoms as they arise and the administration of drugs and sera in accordance with prevalent, and to some extent personal, opinion.

Secondly, certain important therapeutic questions arise in connexion with the complicating factors—pregnancy, labour and the puerperium.

Pregnancy.

On almost every aspect arising out of the association of epidemic encephalitis and pregnancy differences of opinion are rife. Uniformity cannot, therefore, be expected on the question of interrupting pregnancy. Three views are held. Firstly, there is the school, including Hofer,[56] Latzko[62] and Kreiss,[60] which advocates termination of pregnancy in all cases; secondly, there are those who, with Bompiani,[16] would interfere in the more severe cases; thirdly, there is the view taken by Müller,[77] Patek,[84] Marinesco,[68] Bertoloni,[12] Tropl[111] and Amreich[2] that interference is never justifiable. What evidence is there to show which of these three opinions is nearest to the truth?

The condition of the majority of patients remains unaltered after miscarriage or labour, in a few cases the course of the disease changes for the worse after either of these events, while in a few others improvement has been noticed after the uterus has emptied itself. But since the last course is exceedingly rare when compared with the former two, and because it is impossible to foretell on what lines any case will proceed, there is *a priori* evidence against interference with the natural course of a pregnancy.

When attention is turned to those cases in which active treatment has been adopted a like conclusion is reached Two of Hall's cases (4 and 8) were treated by Cæsarean section; their course was similar to the others and showed no difference which could justly be attributed to the treatment, except that in one (4) severe post-operative hiccough proved a troublesome and worrying complication. Although it is true that hiccough has a definite relation to epidemic encephalitis and often occurs during the course of the malady, it is not improbable that in this case hiccough was initiated by abdominal distension after operation. Hall writes of these cases, "In two of the earlier cases, when we had but little information to guide us, Cæsarean section was performed. Happily in both these cases the end results were

satisfactory, but we now know that this procedure was probably unnecessary."

Throughout the literature 20 cases have been found in which pregnancy was artificially terminated in one way or another. A list of these cases is appended, together with the fates of mothers and children and the approximate date at which termination was practised.

Cases in which pregnancy was artificially terminated before viability

Case.	Method of terminating.	Fate of the mother.	Stage of pregnancy reached at time of interference.
Ministry of Health[76]	Induction.	Recovery.	6th month.
Kreiss.[60]	Induction.	Recovery.	3rd month.
Bompiani.[16]	Miniature Cæs. section.	Recovery with sequelæ.	5th month.
Bertoloni.[12]	Induction.	,, ,,	6th month.
Amreich.[2]	Vagl. Cæs Sect.	Death.	6th month.
Valloix.[37]	Induction.	Died during the operation.	5th month.

Cases in which pregnancy was artificially terminated after viability.

Case.	Method of terminating.	Fate of the mother.	Fate of the child.	Stage of pregnancy reached at time of interference.
Price.[90]	Cæs. sect.	Recovered with sequelæ.	Healthy.	Term.
Foulkod.[38]	Induction.	Died.	Healthy.	About 32nd week.
Marinesco.[68]	Cæs. sect.	Died.	Died a few hours after birth.	Between 28th and 30th week.
Pansera.[82]	Induction.	Died.	Dead.	
Santi.[100]	Induction.	Died.	Healthy.	Between 32nd and 34th week.
Banister.[8]	,,	Died.	Healthy.	37th week.
Fino & Fubini [35](1)	,,	Recovered.	Healthy.	35th week.
(2)	,,	Recovered.	Healthy.	Term.
Benthin.[11]	Vag. Cæs. sect.	Died.	Died 20 hours later.	?
Latzko.[62]	Cæs. sect.	Recovered.	Healthy.	Term.
Dimitz.[31]	Induction.	Recovered.	Healthy.	Near term.
Kreiss.[60] (1)	Cæs. sect.	Recovered.	Died soon after.	About 32nd week.
(2)	,,	Recovered.	Healthy.	Term.
Hofer.[56]	,,	Recovered.	Died after a few days.	About 32nd week.

Thus of six cases in which pregnancy was terminated before viability, four recovered and two died, a mortality of 33 per cent. The average mortality among women infected before the sixth month has been shown to be about 46 per cent. At first sight these figures would suggest that benefit accrues from intervention in the early months. But such a deduction is not justified by a consideration of the evidence, in particular that relating to the effects of miscarriage; to reach such a conclusion from a study confined to six cases and against the general weight of evidence is absurd. After all, with one more fatal case the percentages would be almost identical. Moreover, grave doubt must be maintained as to the cause of a successful issue in the four cases which did not die. Can the cure in each case really be attributed to whatever operative procedure was undertaken? The case described in the Ministry of Health s paper[76] was not peculiarly severe and would probably have made a good recovery without induction. Bompiani[16] and Bertoloni[12] are more than doubtful in their cases, although Kreiss[60] is most insistant that the recovery in his was due to the treatment. There is, therefore, in three of the four recoveries more than a doubt as to the cause of the issue. With this knowledge can it honestly be said that induction during the early months yields results which justify its practice? The answer is surely in the negative .

Fourteen pregnancies were terminated after the child had become viable, eight mothers recovering and six dying, a mortality of 43 per cent. four per cent. greater than the ordinary mortality in cases of late infection.

Of course, it can always be argued that induction or Cæsarean section is practised only in the more severe cases which would otherwise have been associated with a considerably higher death rate than the average. That may or may not be true. It seems equally reasonable to suppose that some would have recovered without intervention.

Looking at the cases as a whole it appears that, out of 20 in which pregnancy was interrupted, in 12 the issue was successful; the mortality was 40 per cent., which corresponds very closely with the average death rate of 43 per cent. in the series of 171. In other words, active treatment does not influence the course of the disease in the mother.

The position thus reached appears to be that improvement following uterine evacuation whether natural or artificial, early or late in gestation, is sufficiently rare to make questionable the assumption that it is due to the removal of the products of conception and not to one of the many vagaries of the disease.

Nor is this all. An operation of any sort on patients with acute

encephalitis is not an undertaking to be entered on with a light heart. The advocates of operative treatment are still undecided as to which method is associated with the smallest risk, Hofer[56] favouring Cæsarean section under local anæsthesia at any time after the fourth or fifth month, Fino and Fubini[35] rupture of the membranes, Amreich[2] vaginal Cæsarean section. The fact that operative treatment has its disadvantages is too often overlooked. Valloix,[37] for instance, had a death on the table. The hiccough in case 4 aggravated an already serious condition; it must not be allowed to escape notice that although 12 of the 20 patients treated actively, lived, eight died. Indeed it does not seem going too far to suggest that in some of the fatal cases death was accelerated by operation. Recovery after active treatment is almost always ascribed *ipso facto* to that treatment, death never. Moreover, conservative treatment is more often rewarded with success than failure, another fact which appears to have been overlooked. Its employment, at the lowest estimate, is associated with no higher mortality than the use of surgical measures. In England particularly expectant treatment has yielded very satisfactory results, as shown by the 50 cases reported and analysed in 1922 and by the series reported here.

In these circumstances the submission is made that so far as the interests of the mother are concerned neither induction nor Cæsarean section should be advised in cases of pregnancy complicated by acute epidemic encephalitis.

Cæsarean section is advised by Santi[100] and di Francesco[39] in some cases for the sake of the child. Clearly in the early months the interests of the fœtus are best served by a policy of masterly inactivity. Now of cases infected during the later months of gestation the majority, like those in which infection occurs early, proceed to term; in a few severe cases labour is premature; very, very few die without being delivered. Delivery *per vias naturales* is in general associated with less risk to the infant than Cæsarean section, while the nearer the mother is to term at the time of delivery the greater are the child's chances of survival. There can, therefore, be no indication to interfere for the sake of the child except in very severe cases, of great rarity, in which natural delivery, either before or at term, cannot be expected. Since in these cases the mother is almost certainly doomed there can be no valid reason for withholding Cæsarean section.

Post-mortem Cæsarean section has been performed by Poligone,[88] Kreiss,[60] di Francesco[39] and others. In no case has a living child been extracted. Obviously the operation is one to which there can be no contra-indication or objection.

Labour.

Labour is usually easy and painless. Two important points may be mentioned.

The first of these is the lesson taught by the unfortunate experience of Gaujoux and Bertrou[41] in whose case the infant perished from asphyxia because labour had begun and ended without anybody's knowledge. When it is remembered that the patient was in a hospital ward its importance can hardly be over-estimated. Patients with this disease must be watched most carefully for the onset of uterine contractions.

The second is that if assistance is required every effort should be made to shorten the second stage in order that the mother's resources may be conserved as far as possible.

The Puerperium.

The ordinary puerperal complications, being no more common in cases associated with encephalitis, demand no special consideration.

The only problem which arises is whether or no the infant should be fed at the breast. The answer is probably No, for two reasons. The mother is often enfeebled by her disease, and Parkinsonism often dates from the confinement. Although recovery may appear to be complete the reverse is frequently the case. It is impossible to say, so early, that sequelæ will not develop, and suckling by reducing the maternal resources can only make their appearance more likely and more rapid. To put upon a woman whose energies have already been severely taxed the additional strain of nourishing her infant cannot, in the majority of cases, be justifiable. The risks of milk infection and infection by contagion of the new born have been shown to be very slight, and therefore, on its behalf alone artificial feeding is not to be commended. The mother's interest, however, outweighs that of the baby and the latter should, therefore, be artificially fed.

Summary and Conclusions.

(1) Epidemic encephalitis must be treated as such, apart from the complicating factor of pregnancy.

(2) The question of terminating pregnancy is discussed and the conclusion reached that interference with the natural course of pregnancy is not to be advised, for the following reasons :—

(a) Neither miscarriage nor labour causes any alteration in the course of encephalitis in the large majority of cases. When improvement has been observed the part played by uterine evacuation is uncertain in the extreme.

(b) Conservative treatment was carried out in the majority of the cases reported here with remarkably good results. The two women upon whom Cæsarean section was performed did not appear to benefit as a result. On the contrary one became afflicted with severe post-operative hiccough.

(c) The mortality in the cases of artificially terminated pregnancies collected from the literature is shown to be about the same as the average mortality in all cases. The argument that this increment is due to the severe nature of cases in which active treatment has been undertaken is not admitted, many being no more severe than those which were allowed to proceed to term.

(d) In Great Britain conservative treatment has yielded satisfactory results as shown by the Ministry of Health's Report in 1922.

(e) To operate on patients in the plight of many of the sufferers is a formidable undertaking and likely to be productive of a very high mortality.

(f) Cæsarean section is unnecessary for the sake of the child except in the small group of very severe cases in which hope of saving the mother's life has been abandoned.

(3) Two considerations arise in connexion with the conduct of labour:

(i) Patients should be watched very carefully for its onset, danger lying in the fact that it may be completed without the knowledge of attendants, with consequent risk to the infant.

(ii) The second stage should be completed as quickly as possible, by the use of the forceps if necessary.

(4) The tax of lactation should not be placed upon the mother.

Parkinsonism and Pregnancy.

It matters not what may have been the nature of the acute attack —severe, moderate, mild, or so slight as to have escaped notice at the time—a certain proportion of cases of acute epidemic encephalitis pass by one or another route into the chronic stage. The late manifestations may follow immediately upon the acute attack, or an interval of apparent recovery may elapse before the patient begins to show stigmata of the disease in its chronic form. The period of freedom may last for weeks, months, or even years. On the whole it is more common for such phenomena to become manifest during the twelve months after the acute attack. The number of cases which pass sooner or later into the chronic stage is unfortunately very large. Moreover, it is now too well recognized

that many patients in whom the acute attack attracted no attention, later develop symptoms typical of chronic encephalitis. There are yet others in which no history of any antecedent illness can be traced.

There are many sequelæ of acute epidemic encephalitis and many clinical pictures of the disease in its chronic form. It is not necessary here to enter into a discussion of all the various types, let it suffice to say that that which possesses overwhelming importance is the Parkinsonian syndrome, "compared with which the other developments in adults are few and unimportant"—Hall (personal communication).

The relationships between pregnancy and Parkinsonism have not received very full consideration in the past, the subject to-day being only in its very early infancy. My attention has been called to it by Professor Arthur Hall, who, in a personal communication writes of his eighteen cases: "If these cases represent a true picture of the after-effects of encephalitis in pregnancy, it is indeed an appalling outlook, but one must bear in mind first that the numbers are small, and secondly, that many of them have come under my notice from other districts because of their Parkinsonism. Even allowing for this it seems that the percentage of cases of encephalitis occurring in pregnancy which become Parkinsonian is very high."

There are sundry aspects to this problem, each of which demands as full and as close enquiry as is possible. The subject will, therefore, be discussed under the following heads:—

1. The frequency of Parkinsonism in those who fell victims to acute epidemic encephalitis while pregnant, or during the puerperium.
2. The date of onset of Parkinsonism.
3. The effects of pregnancy on Parkinsonism.
4. The influence of Parkinsonism on pregnancy, labour and the puerperium.
5. The child of the Parkinsonian mother.
6. Parkinsonism, amenorrhœa, impotence and sterility.
7. Treatment.

1. *The frequency of Parkinsonism in those who fell victims to acute epidemic encephalitis while pregnant or during the puerperium.*

It is to be noticed that of the 171 cases collected from the literature and classified previously as "recovered," many were in reality only partial recoveries. These will be found referred to as "recovered with sequelæ" to the number

of twenty-eight. This, of course, is less than the average for non-pregnant cases, for of the latter about a quarter eventually become Parkinsonian. It is, however, to be remembered that in the majority of instances the after-histories of the patients are traced at longest for only a few months and often only for a few weeks. To attempt to form any estimate under such conditions would be futile.

There remains the evidence afforded by the twenty cases reported here in which encephalitis during its acute phase complicated pregnancy. Of these, sixteen became Parkinsonian, while one of the remaining four (Victor Bonney's case) has developed other residua. Sixteen out of twenty represents an incidence of 80 per cent. It is true that the series is small and that many of these patients came under observation for the first time on account of their Parkinsonism. But even so, the figure is extraordinarily high. Putting such cases aside and considering only the nine which occurred in Sheffield itself in 1924, seven became Parkinsonian—77 per cent. The average incidence of this sequela among all women between the ages of 16 and 45 in the epidemic during which those nine cases occurred, was only 29 per cent. at the end of 1925.[72] It is, therefore, justifiable to conclude that women infected while pregnant in the Sheffield outbreak of 1924 were more liable to develop Parkinsonism than those in whom the acute attack occurred without pregnancy. It is impossible to go further at the present time.

2. *The date of onset of Parkinsonism.*

The occurrence of acute epidemic encephalitis during pregnancy does not materially affect the time taken for establishment of the Parkinsonian syndrome.

Pregnant, like non-pregnant, women show considerable variation in the time taken for the establishment of definite manifestations which may be of early onset following immediately upon the acute phase, or may be late and delayed for an interval of months or years.

But pregnancy appears to affect the date of onset in two ways. Firstly, Parkinsonism may appear shortly after the termination of the pregnancy during which the acute attack occurred. The onset then, truly enough, is early but the definite relation which it so frequently bears to the confinement makes it worthy of special consideration. Secondly, Parkinsonism not infrequently first becomes evident at some time during a subsequent pregnancy. This is true of cases in which pregnancy and the acute attack coincided, as well as of those in which the acute phase was not so complicated.

Cases of Parkinsonism in relation to pregnancy may therefore be divided into four groups :—

(a) Those in which the onset is early, there being no special relation to the confinement.

(b) Those in which the onset is late, there being no special relation to subsequent pregnancies.

(c) Those in which the onset occurs soon after the termination of the pregnancy which was complicated by acute epidemic encephalitis.

(d) Those in which the onset occurs during the course of a subsequent pregnancy.

(a) *Those in which the onset is early, there being no special relation to the confinement.*

The earliest Parkinsonian symptoms may become manifest immediately after, or even just before, subsidence of the acute attack. This gradual merging of acute and chronic stages is not very common in non-pregnant patients (Hall and Yates[50]).

It is always difficult even for eye witnesses accurately to date the onset of so insidious a malady as Parkinsonism, still more difficult when the information is obtained second-hand by reading descriptions of cases. There is, however, no doubt that in case 4, as well as in those of Klippel Baruk,[59] Fort,[37] Forget,[36] del Sole[109] (2) and Bompiani,[15] a definite onset took place within the three months following the primary attack. There is, moreover, no reference, in the reports of any of these women, to an intervening period of apparent health. This being the case, it seems fair to conclude that an early onset is not uncommon when Parkinsonism is secondary to acute encephalitis during pregnancy. It is readily granted that this opinion may in the future be proved wrong and that it is based rather on a general impression gained by a perusal of the available literature than upon accurate statistical evidence which is not at the present time available.

(b) *Those in which the onset is late, there being no special relation to subsequent pregnancies.*

Symptoms of Parkinsonism may be delayed for a few months during which the patients enjoy apparent health; this interval in the pregnant, as in the non-pregnant patients (Medical Research Council Special Report No. 108, 1926), is usually not greater than 18, nor less than six months (cases 6, 14, 16), though it may be prolonged to two or more years (cases 11 and 17, d'Andrea's case[4]); prolongation to as long as four years has been once reported by Fort.[37]

(c) *Those in which the onset occurs soon after the confinement following the termination of the pregnancy which was complicated by acute epidemic encephalitis.*

It has been observed by Hall[48] that not uncommonly Parkinsonism appears to date from the confinement or soon after. Cases 1, 3, 5, 7, 9, 10 and 12 appear to be of this nature; Bompiani,[15] Forget,[36] Rathery and Cambessédès[92] all record cases in which chronic symptoms appeared within three months of the confinemen. Gordon-Holmes[34] reports a case in which Parkinsonian symptoms first appeared within half an hour of a difficult labour. Of course, it can always be argued that the onset of Parkinsonism at this time is a mere coincidence, and that the number of cases is too small to justify far reaching conclusions. It is always proper to adopt a cautious attitude in problems of this nature, but it is surely better to deduce what conclusions are possible from admittedly few data than, for the sake of caution alone, to mark time until an adequate number of cases has been published. That deductions made to-day will be proved wrong to-morrow need be no deterrent, for it is only thus that science can progress. If the puerperium is favourable to the onset of Parkinsonism the above suggestion that early onset is common following an acute attack with pregnancy clearly receives support. It will subsequently be argued that aggravation of pre-existing chronic manifestations is especially common following subsequent confinements, which lends further support to the opinions here expressed. An early onset of Parkinsonism seems not uncommon, an onset after the same or subsequent confinements occasionally occurs; and aggravation after subsequent confinements will be shown later to be common, a series of observations which suggest that the puerperium, for some reason, presents conditions suitable to the activities of the virus of the disease in its chronic form.

(d) *Those in which the onset occurs during the course of a subsequent pregnancy.*

Parkinsonism may make its first appearance during the course of a subsequent pregnancy. This is equally true whether the acute attack occurred with or without pregnancy, and is remarked upon by Hall[48] who, in his book, refers to three cases in which the appearance of Parkinsonism coincided with the occurrence of pregnancy. Two of these cases (Meyer[74] and Lévy[66]) were of Continental origin and were published in 1921, the third was his own. In 1920, Valente and David[57] described a case of "encephalitis lethargica of the chronic Parkinsonian type with pregnancy." It seems possible that this was the sequel of an unnoticed primary attack. The preg-

nancy in their case, as in the others at present under discussion, proved the undoing of their patient. Since those early days this observation on the occasional first appearance of Parkinsonism during the course ot a pregnancy has received confirmation. In one of the cases reported by Strecker and Willey[107] typical symptoms of the Parkinsonian state developed during the last few days of a pregnancy which occurred two years after an abortive acute attack. A further pregnancy aggravated symptoms. Fort[37] speaks of a woman who completely recovered from acute encephalitis and remained well until the fourth month of her first pregnancy four years later. Mrs. T. (case 17) recovered from a primary attack of encephalitis in the spring of 1920; she became pregnant again two years later, and soon she passed into the Parkinsonian state. Berkeley and Cockayne's case (19) is very similar.

3. *The influence of pregnancy on Parkinsonism.*

That pregnancy occurring in one who is already a Parkinsonian is a happening attended by untoward results has been noticed on more than one occasion by American and European writers. The fact has been remarked by Hall.[48]

The unfavourable character of this influence was evident in each of the five author's cases in which pregnancy was complicated by Parkinsonism (5, 11, 17, 19 and 21). In case 5 the patient, though unable to do her housework during the 18 months following the acute attack, was capable of washing and dressing herself. A second confinement at the end of those 18 months caused an accentuation of her residual phenomena, the ability to wash and dress herself disappearing. Very similar is case 11; recovering after the delivery of her first child in July, 1924, this patient remained in apparently good health until the birth of another infant in May, 1926, whereafter she rapidly developed typical Parkinsonian symptoms. Case 17 was one of a young woman in whom the syndrome became definitely marked soon after the advent of a second pregnancy in the summer of 1922. Since the acute attack in November, 1920, during the early months of her first pregnancy, her health had been sufficiently good to permit of her carrying out her ordinary daily tasks. A third pregnancy in November, 1924, considerably aggravated her condition. It is noticeable that in case 5 the already present Parkinsonism became exaggerated after the second confinement, while in case 11 the syndrome in a similar way made its first appearance after a second confinement. In case 17 an aggravation of symptoms took place during the early months of a second pregnancy, and a further aggravation soon after the occurrence of a

third. In case 19 the earliest manifestations appeared during the first few months of a second pregnancy two years after an acute attack of encephalitis, and after the second confinement a noticeable change for the worse took place. The already present Parkinsonian symptoms were aggravated on the occasions of two pregnancies in case 21, aggravation bearing, according to the relatives, a very definite relation to the early months of gestation and to the puerperium.

Judging from these five cases there appear to be two danger periods during which epidemic encephalitis in its chronic form is liable to undergo exacerbation. The first is during the early months of a subsequent pregnancy, the second, following a further confinement. Admittedly it is not always easy to determine exactly when symptoms increase in severity, and that such increase is due to the pregnancy or confinement is necessarily difficult to prove. However, in the above cases the evidence is fairly convincing. In all a marked and relatively sudden change took place in symptoms which were previously stationary or progressing, till then, very slowly. del Sole[109] in 1924 observed how the disease assumed its chronic form during the first half of gestation in three cases. Two of his patients had suffered from acute encephalitis during previous pregnancies, at the termination of which there had been a cessation of the disease, with at least an apparent diminution in symptoms until the occurrence of further pregnancies. His third patient was not pregnant at the time of the acute phase, but became so after a slight improvement. Her condition rapidly became worse during the early months of this pregnancy. All these cases succumbed soon after premature labour between the eighth and ninth months. In del Sole's cases, after the preliminary accentuation during the earlier months, the disease became stationary until the time of the confinement, after which a further exaggeration occurred. These cases are in keeping with those to which reference is made above and receive general support from the literature. Stursberg's[108] patient exhibited a typical recrudescence during the second month of a pregnancy which ensued six months after recovery from moderately severe encephalitis. Improvement immediately followed induction at the eighth week. In the writings of Bompiani[16] there will be found four cases which have a bearing on the problem. In the first the manifestations of Parkinsonism appeared during the fifth month of a succeeding pregnancy, and gradually became worse until the eighth month, when she went into labour. Thereafter a temporary improvement occurred which was followed by an exacerbation three weeks later. This is one of the few recorded cases in which epidemic encephalitis has been asso-

ciated with toxæmia of pregnancy. In the second case Parkinsonism was first noticed during the third month of pregnancy two years after epidemic encephalitis . The third case was that of a woman who had suffered from slight Parkinsonian symptoms for the two years following a typical acute attack. During the early months of her next pregnancy her relatives noticed a slight exaggeration in all her symptoms; a change for the better followed until the tenth day of the puerperium, when her Parkinsonism became more marked than ever. The fourth of Bompiani's[16] cases of importance in this connexion concerns a young woman who became Parkinsonian during the fourth and fifth months of a first pregnancy. The acute attack, which was of moderate severity, had taken place three years previously. Bompiani[15] describes her condition at the fifth month, and is careful to note that from that time until the termination at full time her signs and symptoms underwent no change. The subsequent history of this patient would be interesting, but unfortunately it is wanting. Pitimada's[86] case is of interest in that three successive pregnancies aggravated a Parkinsonism syndrome ; of which the symptoms became less marked after each of the three normal confinements at full time. This author notices in particular that post-encephalitic rigidity and hypertonia are exaggerated during subsequent pregnancies. The reported account does not state the stage which the pregnancies had reached when the symptoms as a whole began to show evidence of accentuation. The author concludes that each of the three pregnancies caused an exacerbation, and pays special attention to the rigidity which, he says, invariably underwent a gradual increase during pregnancy, was always most marked during the later months, and improved after the confinements. If this observation applies with equal force (Pitimada[86] does not indicate that he believes it does so apply) to the other residual symptoms, then the rule, that an initial augmentation during the early months is always followed by a period of no alteration, evidently has exceptions. Fort[37] twice noticed aggravation early in pregnancy and three times during subsequent puerperia. Two other cases complete the available references. Strecker and Willey[107] noticed an exaggeration of symptoms following normal delivery at term in two Parkinsonian patients.

The literature is thus replete with examples which show some relationship between pregnancy or the puerperium on the one hand and post-encephalitic Parkinsonism on the other. While this relationship may to-day be taken as proved beyond all reasonable doubt it is well to remember that there is another side to the question, and that there may have been a tendency to amplify the influence of pregnancy on those who suffer from the disease in the

chronic form. It will be remembered that the earlier writers erred in this way when dealing with the acute phase. There can be no doubt, for instance, that Cæsarean section was in some cases resorted to unnecessarily because of the unduly grave prognosis which was at that time always given, in accordance with the prevalent view. In the later light of more experience this view has been shown to be erroneous. It is, therefore, expedient to see what evidence, if any, is forthcoming on the other side; in other words, are Parkinsonian symptoms ever less in evidence after a subsequent pregnancy? In this connexion it is well to remember that the cases referred to above are just those which would be expected to find their way into the records. They are spectacular; they strike the imagination; they are far from being wholly without foundation; they form a fruitful field for those who like to speculate on their causation; and finally they are to be expected. Is it remarkable that the stress and strain of pregnancy superimposed upon one who is already the subject of an insidious and chronic disease, actually or potentially present, should so diminish the resistive powers as to allow the virus, which apparently never dies, to become more potent at the unfortunate patient's expense? But in spite of this anticipation of their occurrence they are the most probable cases to be reported. Writers rarely deal with what may be called negative cases. Many Parkinsonian women must have borne children with no ill effects. Parkinsonism is common, pregnancy more common, Parkinsonism does not cause sterility, yet when examples are sought their scarcity at once becomes apparent. Only five cases have been found, those of Bompiani,[16] Fort,[37] Guillain and Gardin,[44] d'Andrea[4] and Henneberg.[54] The last named author noticed a distinct improvement during the puerperium. While Santi,[100] Lévy,[66] Bompiani[16] and Sturmer, quoted by Bompiani[16] are convinced of the unfavourable influence of pregnancy on pre-existing Parkinsonism, Fort[37] remains an unbeliever, thinking the evidence as yet too slight. Though few in number, these cases are sufficient to show that women who are the subjects of Parkinsonism can go through pregnancy and labour without necessarily becoming worse. It is true that records of such cases are relatively rare, and that the converse appears to be the rule. The fact that these women have occasionally given birth to children without aggravation of their symptoms has some prognostic signification and should be called to the mind of the doctor who treats such patients.

Thus far, then, it has been shown that pregnancy aggravates pre-existing Parkinsonism, that not infrequently Parkinsonism appears for the first time during the course of pregnancy, while

in a few authenticated cases gestation has come and gone without untoward effect. It remains to show whether there is any particular time in pregnancy, labour or the puerperium during which aggravation is specially common.

On critical examination the statement that the symptoms become aggravated early in pregnancy is found to be not very far from the truth. A second exacerbation is often observed after the confinement or may occur without preliminary exaggeration during the earlier months. Curiously enough, improvement after the confinement in spite of a previous exacerbation is occasionally noticed. These facts can be seen from the following tables: —

Aggravation of Parkinsonism during Pregnancy

Cases.		Approximate stage of pregnancy or puerperium during which aggravation was observed.
Hall.	5.	After confinement.
Hall.	11.	,, ,,
Hall.	17.	Early in pregnancy.
Berkeley and Bedford.	21.	Early in pregnancy and again after the confinement on two occasions.
del Sole.[109]	1.	First to 4th months.
	2.	First to 5th months.
	3.	Early in pregnancy.
Bompiani.[16]	1.	5th to 8th month.
	2.	3rd month.
	3.	Early in pregnancy and again after confinement.
	4.	4th and 5th month.
Strecker and Willey.[107]	1.	After confinements on two occasions.
	2.	After confinement.
Pitinada.[86]		Hypertonicity always worse in the later months of three successive pregnancies.
Fort.[37]	1.	After confinement.
	2.	Worse at the beginning of her second pregnancy, with very marked exacerbation after that confinement; Parkinsonism had appeared about a year before, during her first pregnancy.

Onset of Parkinsonism during Pregnancy.

Case	Approximate stage of pregnancy.
Hall. 17.	Early in pregnancy.
Berkeley and Cockayne. 19	Early in pregnancy.
Meyer.[74]	Parkinsonism became well developed by the sixth month. Considerably greater aggravation one week after delivery.
Lévy.[66]	During the first half of gestation.
Valente and David.[57]	Second month.
Strecker and Willey.[107]	Immediately after confinement.
Fort.[37]*	Fourth month.
Gordon-Holmes.[43]	Within half an hour of a difficult confinement.
Fort[37] (Beriel's case).	Early in her third pregnancy, return of slight symptoms but became marked after confinement.
Fort[37] (Chauffard's case).	Fourth month.

*The same case as Fort 2 in previous page.

Parkinsonism Worse:

Case.		Before the fifth month.	Between the fifth month and labour.	After Confinement
Hall.	5.			x
Hall.	11.			x
Hall.	17.	x		x
Berkeley and Bedford.	21.	x (twice).		x (twice).
del Sole.[109]	1.	x		x
	2.	x		x
	3.	x		x
Bompiani.[16]	1.			x
	2.	x		
	3.	x		
	4.	x		x
Pitimada.[86]			x (three times).	
Strecker and Willey.[107]	1.			x (twice).
	2.			x
Fort.[37]				x

Parkinsonism Appeared:

Case,	Before the fifth month.	Between the fifth month and labour.	After Confinement.
Berkeley and Cockayne.	x		x
Meyer.[74]	x		x
Lévy.[66]	x		
Valente and David.[57]	x		
Strecker and Willey.[107]			x
Gordon-Holmes.[43]			x
Fort.[37]	x (twice).		x (twice)
Fort[37] (Beriel's case).	x		x
Fort[37] (Chauffard's case).	x		

Here, then, are 24 cases in which the Parkinsonian syndrome has been aggravated during, or made its first appearance with, pregnancy. In 15 the aggravation or onset took place during the first half of gestation, and in ten of these 15 a further exacerbation was observed soon after the confinement. Adding six in which the symptoms became worse during the puerperium without the previous exacerbation and two in which they appeared then for the first time, it will be seen that on 18 occasions Parkinsonism has undergone a change for the worse or first become manifest during the period immediately following labour. In one case only were the effects observed during the second half of pregnancy. These figures, like so many others relating to chronic encephalitis with pregnancy, are admittedly small, yet their character is such that it seems not unjustifiable to conclude that Parkinsonism is particularly prone to exacerbation during the early months of pregnancy or in the early days of the puerperium. Is there any reason why these two periods should be selected?

It is not surprising that aggravation should be common during the early months. . The onset of pregnancy in these patients must surely tax their resources considerably. It is known that pregnancy throws a definite strain on all the organs. This is usually credited with being due to a slight toxæmia as manifested biochemically by blood and urine changes, and clinically by the medley of conditions grouped, for want of better term, under the heading "toxæmias of pregnancy." While it is true that these phenomena are more common during the second half of gestation there can be no doubt that the growth of the ovum from its very beginning does cause a slight metabolic upset, as witnessed by the physiological vomiting during the early months. It can readily be understood that a Parkinsonian woman is unequal to the extra demands made upon her economy, and therefore her symptoms

become more marked. The additional call begins as soon as the ovum is fertilized; it is, therefore, to be presumed that at that very moment aggravation of the disease commences, but on account of the extreme slowness in development of all Parkinsonian phenomena a few weeks or months elapse before aggravation becomes clinically apparent. The contention that after preliminary exacerbation the disease becomes stabilized till after labour, has not attracted much attention. It is, indeed, quite conceivable that by the end of the fifth month these patients have, as it were become acclimatized to the pregnant state, and their encephalitic symptoms remain stationary at the level reached during those first five months, until the occurrence of labour and the commencement of lactation make still further demands to which their enfeebled constitutions are unable adequately to respond.

Regarding those cases in which the confinement appears to be the determining factor, there are at least three possible explanations. Firstly, it may be, as suggested by certain Continental writers, that the fœtus in utero removes through the medium of the placenta toxins from the maternal blood; after labour this route of excretion is no longer available. Secondly, the effort of delivery may be the determining factor. Thirdly, it may be that the demands of lactation are too great for these women.

The first hypothesis postulates that the change so common after confinement is due to the removal by the birth of the child of one of the channels of maternal excretion. This hypothesis has one attraction—nobody can in the present state of knowledge disprove it! But to establish such an hypothesis it would be necessary, firstly to prove the presence of toxins in the mother's circulation, and secondly that they can cross the placenta. It has already been shown that transplacental passage of the virus during the acute stage is a possibility and has been proved by post-mortem evidence to have taken place in Marinesco's[68] celebrated case. But this author was dealing with the disease in its acute form, and he himself admitted that such passage, though possible, is rare. Transmission to the infant, *via* the placenta, has never been established in the case of chronic encephalitis; even admitting that it might occur, it must be excessively rare, for the children are usually healthy at and after birth, and exhibit no suggestive symptoms. To argue that toxins capable of causing a severe exacerbation in the mother's condition were harmless to the fœtus would be absurd. While it is true that occasionally the children are stillborn it has yet to be shown that their death is due to the virus of epidemic encephalitis. To prove this it is necessary to produce post-mortem evidence from the examination of the fœtal

and infantile nervous systems. Such evidence is absent, and the theory may be discounted.

There is much to said in support of the second view, that Parkinsonism becomes aggravated during the puerperium because of the generally lowered resistance. There is no doubt that the puerperium is a time when the powers of resistance are low. The ease with which women become infected with streptococci during childbirth, and the rapidity with which such infection spreads exemplify this. The fact that autogenous infection from a latent septic focus far from the pelvis occurs every now and then supports the contention. A woman may pass through pregnancy without a single abnormal sign, and yet after labour develop an alarming and rapidly fatal blood infection despite the most meticulous and rigid aseptic precautions on the part of those responsible for the confinement. In such cases a focus may be found somewhere in the body, whence the organisms were derived.

There is something about the puerperal state peculiarly suitable to the multiplication of such organisms and to the exaltation of their virulence. Patients with pulmonary tuberculosis often pass safely through pregnancy and labour but rapidly become worse during the puerperium; the analogy between this and chronic encephalitis is apparent. The underlying causes of this sensitiveness to organismal attack after childbirth are not known, but in all probability there are several factors which combine to reduce the reserve of stamina in women at this period. Labour itself, however easy it may appear, must be a strain on any woman; efforts are required of her, sometimes greater, sometimes less, to accomplish the birth of her infant; during labour she loses blood, not much perhaps, but sufficient to help to turn the scale against her when infection is present and has to be fought. Berkeley and Bonney[13] refer to labour as a process accompanied by self-inflicted wounds, and to the puerperium as the period of their healing. During the days succeeding childbirth the bodily economy is specially directed to the repair of these wounds. Changes are concomitantly taking place, which bring about involution of the uterus and the secretion of milk. In fact the puerperium, although often regarded as an anti-climax, is a time when the resources of a woman are being considerably taxed, the defensive mechanism is at a low ebb, and any latent or chronic infection has an opportunity of gaining ground. The result is the same whether that infection is the tubercle bacillus, the streptococcus of pyorrhœa alveolaris or the virus of chronic encephalitis.

It might be argued that if labour was the cause of puerperal exacerbation or appearance of Parkinsonism, labour would be

expected to be difficult and prolonged, but on the contrary, the large majority of Parkinsonian women who have been confined have had easy labours. The only divergence from the normal appears to be an absence of the physical pain associated normally with the contractions of the uterus. It is true that occasionally delivery with the forceps has been practised for inefficient expulsive powers, Bompiani[16] deeming it necessary to interfere in this way on two occasions. This, however, is the exception rather than the rule. As in the case of acute epidemic encephalitis authorities are agreed that in the large majority of cases labour is normal, and the puerperium devoid of complications. Instrumental deliveries are no more common in Parkinsonian women than others.

Such an argument misses the point. It is not suggested that labour, *qua* labour, is the determining factor in any aggravation the disease may undergo during the days which follow. Furthermore, were labour itself the aggravating factor the symptoms would be expected to increase in severity during the first or second stages or immediately after the third. The time of onset of Parkinsonism, or the moment at which its manifestations increase, is always difficult to fix with accuracy, but even so the occurrence of such concomitantly with labour would certainly have attracted attention.

It is not, however, suggested that the confinement itself is the cause of any aggravation which may take place during the puerperium, for that is only one of several factors which combine to reduce the resistive powers of these patients. From the very beginning of pregnancy there is, as it were, a chain of events working against the Parkinsonian woman. The pregnancy itself takes something out of her; to this her powers may be equal, in which case no untoward happenings occur, or it may prove more than she can bear, in which event some change in her condition takes place soon after she becomes pregnant. Her energies having already been taxed by carrying her child, a further call is made upon her resources by its birth; having delivered her child her energies are directed to the healing of the labour wounds, to the involution of the uterus (surely an active, not a passive, process), and finally to the support of her infant by lactation.

By the time the puerperium is reached the unfortunate woman has little power to fight the disease, which, therefore, undergoes exacerbation. The same is often seen in chronic cardiac disease with pregnancy, compensation frequently failing just after labour has been accomplished with apparent safety.

There remains for consideration the third possibility—the demands of lactation are more than these patients can stand. *A priori* it is not difficult to understand that a mother the subject of an

insidious and often progressive disease is unequal to the call made upon her economy by a growing and thriving baby. It is well known that sufferers from any chronic disorder, such, for example, as pulmonary tuberculosis, are not fitted to supplying the needs of their infants in addition to their own. It is likewise true that mothers in a very bad bodily condition produce milk in sufficient quantity and quality for their offspring. But in guarding the welfare of the progeny, nature exacts a toll from such individuals—they secure the future of their race at the cost of their own health. From the outset this third hypothesis appears not unreasonable. Indeed there can be no doubt that lactation does act in combination with the other factors already discussed. That it is not the sole cause of these puerperal exacerbations is shown by their occurrence in some cases in which the children have from birth been fed artificially or in which they have been stillborn (del Sole[109]). Moreover, weaning has not always caused an improvement (Bompiani,[16] Klippel and Baruk,[59]) as it would, were lactation the only agent acting.

Summary and Conclusions.

1. In five cases from the present series (Hall and Berkeley), Parkinsonism complicated pregnancy. The symptoms in all five became more pronounced during gestation, confirming earlier experience.

2. Symptomatic aggravation occurred on each occasion either early in pregnancy or after confinement, an observation to which support is lent by other cases from the literature.

3. Although, in general, pregnancy has an unfavourable influence on Parkinsonism, cases are quoted which show that women with chronic encephalitis sometimes pass through pregnancy and labour without alteration in their disease.

4. Out of 24 cases in which the Parkinsonian syndrome was aggravated during, or made its first appearance with, pregnancy, in 15 the aggravation or onset occurred early in gestation; in 10 of these 15 a second exacerbation was observed early in the puerperium. In all, a change for the worse after confinement has been noticed on 18 occasions. These figures speak strongly in support of the view enunciated above.

5. The reasons for the selection of these two periods are discussed. It is suggested that pregnancy, by making additional calls upon the mother, lowers the general resistance and very soon causes the disease to become geared at a higher level; this is maintained until the factors acting at the time of the confinement cause a further change for the worse.

4. *The influence of Parkinsonism on pregnancy, labour and the puerperium.*

While agreement seems to have been reached upon the unfavourable effects of pregnancy on Parkinsonism the converse proposition remains in a rather unsatisfactory state.

There is a general consensus of opinion with regard to labour and the puerperium in these women, but, on the other hand, when the question of pregnancy is investigated there are found to be two opposed schools of thought. The position appears to be that labour and the puerperium are little influenced by chronic encephalitis, whereas pregnancy according to some is affected by the disease in that premature labour is of common occurrence; according to others pregnancy proceeds to term in the ordinary way.

Pregnancy.

If it could be shown that the toxæmias of pregnancy were more common or that miscarriage was more frequent it would be justifiable to infer that Parkinsonism was harmful to pregnancy just as pregnancy is harmful to Parkinsonism. It has never yet been suggested that these women are more prone to toxæmic manifestations than others, although occasional cases have been reported. Bompiani[16] refers to two in which œdema and vomiting together with albuminuria made up a characteristic picture of toxæmia. He concludes that the intoxication of these patients was due to the virus of encephalitis, acting in combination with the pregnant state. Stern[106] found liver changes at autopsies on Parkinsonian patients apart altogether from pregnancy. Bompiani[16] therefore argues that the additional strain thrown on the liver, already incompetent, by the pregnancy, causes the appearance of toxæmic manifestations. The argument is attractive and the reasoning logical; but it is nevertheless a fact that toxæmia plus chronic encephalitis is rare. There is no reason to deny Bompiani's[16] explanation in cases in which the two do occur together, and no great harm is done by thus attributing the toxæmia to the combined effect of the two conditions. At the same time, on account of the relative infrequence of the ordinary toxæmias in Parkinsonian patients, there seems equal justification for the view that their pathology is the same whether the Parkinsonian syndrome is present nor not. In other words, there is no reason to assume that Parkinsonism plays any part in the production of toxæmias of pregnancy.

It has already been stated that divergent views are held upon the question of premature labour. Both del Sole[109] and Bompiani[16]

incline to the view that chronic encephalitis is a cause of premature birth, the latter although he only noted its occurrence once in a series of seven cases, and the woman who miscarried was a multipara with 11 children and several previous miscarriages. However it is perfectly true that it does sometimes occur, and since its occurrence is usually associated with the more severe cases, it seems more than probable that it is due to the disease. On the other hand it cannot be granted that the average Parkinsonian woman is especially liable to go into labour before full time. Reference to the following table which contains most of the reported pregnancies in Parkinsonians will make this evident :—

Case		Onset of Labour.
Hall.	5.	Term.
Hall.	11.	Term.
Hall.	17.	(1) Term.
		(2) Seventh month.
Berkeley and Cockayne.[19]		Term.
Berkeley and Bedford.	21.	(1) Term.
		(2) Term.
del Sole.[109]	1.	Between the 8th and 9th months.
	2.	,, ,, ,,
	3.	,, ,, ,,
Bompiani.[16]	1.	Term.
	2.	Artificial termination about the 5th month.
	3.	Term.
	4.	7th month.
	5.	Term.
Strecker and Willey.[107]	1.	Term.
	2.	Term.
Pitimada.[86]		(1) Term.
		(2) Term.
		(3) 20 days before expected date.
Meyer.[74]		Term.
Lévy.[66]		Term.
Valente and David.[57]		Term.
d'Andrea.[4]		Term.
Henneberg.[54]		Term.
Guillain and Gardin.[44]		Term.
Fort.[37]	1.	(1) Term.
		(2) Term.
	2.	(1) Term.
		(2) Term.
	3. (Beriel's Case).	Term.

Case		Onset of Labour.
	4. (Chauffard's case).	Death of the mother before delivery.
	5. (Rhenter's case).	Term.
Gordon-Holmes.[43]		Term.

There were then 34 pregnancies among 28 patients. Excluding the case in which pregnancy was terminated, it can be seen that 27 pregnancies out of 33 went satisfactorily to term. In five labour was premature between the seventh and ninth months; one died undelivered, 81.5 per cent. normal full time deliveries, or roughly a ratio of one premature labour to four confinements at term.

(The third confinement in Pitimada's[86] patient is not regarded as premature, being just within the limits of calculable error).

It has already been remarked that all five cases in which delivery occurred before term, were more than usually severe. Case 17 was most certainly of this nature; del Sole's[109] patients all died a few weeks after confinement; Bompiani's[16] case was one associated with albuminuria and toxæmic vomiting; the toxæmia in all probability played some part in determining the premature onset of labour. This case is of particular interest in that after delivery the vomiting and headache ceased, whereas the nervous manifestations became considerably aggravated early in the puerperium—regarding the toxæmia, delivery benefitted the patient, regarding the encephalitis it did not prevent the common exacerbation during the succeeding days.

It is therefore to be concluded that Parkinsonism does not alter the course of pregnancy except in its more marked forms when premature birth towards the end of gestation may occur.

Labour.

The course of labour is little influenced by the presence of the Parkinsonian syndrome, the only divergence from the normal being either a diminution in or an absence of the physical pain associated with contractions of the uterus; both del Sole[109] and Bompiani[16] remark this fact. The former is of opinion that labour is exceptionally easy and painless, but he draws this conclusion from a study of three cases in which the infants were all premature. Naturally labour is easy with such small and ill-developed children as those to which his patients gave birth. Bompiani[16] on the other hand considers that, on the whole, the forces are less competent

than normal, and that therefore, instrumental delivery is more commonly required; he found it necessary to employ the forceps in three of five first labours, the indication being undue prolongation of the second stage owing to inefficiency of the natural forces. This indication has led others to a forceps-delivery in Parkinsonians. It is also, incidentally, a common indication apart from Parkinsonism.

The records point strongly to normal first, second and third stages in the large majority of cases. When delivery by the forceps has been practised the patients have been, with the exception of d'Andrea's[4] case, primiparæ. There is complete absence from the literature of any reference to post-partum hæmorrhage, or any other complication, common or uncommon. In short, labour in these people is as labour in others, save that their physical and mental suffering is, if anything, slightly diminished.

The Puerperium.

What has been said of labour applies even more strongly to the puerperium.

Summary and Conclusions.

(1) *Pregnancy* is not usually affected by the concomitant presence of Parkinsonism.

In a series of 34 collected pregnancies, including the author's group, 27 went satisfactorily to term—81.5 per cent.

Premature birth near full time is of only occasional occurrence, and is limited to the more severe cases.

(2) *Labour* is easy in Parkinsonian patients and associated with less pain than in normal individuals.

(3) *Puerperal complications* are very uncommon.

5. *The child of the Parkinsonian mother.*

Parkinsonism in the mother does not appear to have any effect upon the child. The vast majority of children are of normal weight, healthy, and thrive. Their subsequent history when traced is negative. Thus the three infants born to Berkeley's Parkinsonian patients remain healthy. One child is now two and a half years old, another two years, and the third six months. Strecker and Willey[107] traced infants to the fourth and fifth years without observing any suggestive signs. Often, as in the case of acute encephalitis, there is no such record, authors contenting themselves with the observation that until the time of the mother's discharge from hospital the infant developed along normal lines. The

absence of further information concerning these children is not without importance, for it can hardly be that, in these enlightened days of elaborate "follow up" systems, the medical men in charge of Parkinsonian patients would not trouble to enquire further into the histories of the children. It is by no means improbable that they would not communicate regarding normal infants, having once reported their good health; certain it is that they would not be slow to notice anything amiss.

There is, however, a minority of cases in which the children have either been born dead or have survived only for a few days. With one exception all these infants have been premature; del Sole's[109] three cases, for instance, were all 34 week babies, the second confinement in case 17 took place considerably before term; in one of Bompiani's[16] cases the child died eight days after induction at the seventh month. Prematurity at the 34th week is associated with a sufficiently high fœtal mortality to make it unnecessary to call in extraneous causes to account for the death of these infants. Many children born at this stage of gestation succumb within a few weeks of birth. If their death was due to infection *via* the placenta fœtal death before term would be expected to occur occasionally; in the case of chronic encephalitis the infants invariably survive a few hours or days before succumbing. This does not appear to have attracted attention. Reference to the cases mentioned above will render this clear. The exception to the rule that infantile mortality is confined to premature children is a case from Bompiani's[16] series. This patient in 1920 had a typical acute attack of epidemic encephalitis with consecutive Parkinsonism; in 1922 she became pregnant, and was delivered of an apparently healthy child at term. The infant was put to the breast, after seven days became somnolent, and died on the 11th day with high fever. Bompiani[16] suggests that here is an example of infection conveyed through the mother's milk. It may be so. Before accepting this it would be necessary to show firstly that death was due to epidemic encephalitis, secondly that the child was not infected before birth, and thirdly that there was no other possible source of infection. There is no record of a post-mortem examination of the infant's body, and therefore, it cannot be said with certainty that death was due to encephalitis; the question as to the mode of infection does not in these circumstances arise.

The general weight of evidence goes to show that the child does not suffer as the result of chronic encephalitis in the mother except in so far as that disease plays a part in the production of premature infants. The likelihood of premature labour has already

been shown to be reasonably small, the child's chances are, therefore, correspondingly good.

6. *Parkinsonism, amenorrhœa and sterility.*

In only two cases throughout the literature has amenorrhœa been observed in connexion with Parkinsonism. One of these, that of Forget,[36] was of considerable severity and the patient died with hæmatemesis six months after the cessation of the periods, and three years after the acute attack; the other, of Bompiani,[16] was one in which the syndrome was definite but slight, the menses were sometimes scanty, at others abundant, the patient became pregnant two years after the acute attack showing that her sexual organs were sufficiently normal to produce a child. Amenorrhœa in these patients is, therefore, a rarity and is not to be expected; that it does occasionally occur is shown by the above cases. Chronic infections and wasting diseases, such as tuberculosis, are capable of causing menstrual suppression; in an analagous manner chronic encephalitis at times produces a like result.

It is evident that Parkinsonism does not cause sterility, nor is there anything to suggest that these women are more than usually prolific. It is reasonable to suppose that in some women conception does not occur because their mental and bodily infirmities may prohibit coitus. Some of the patients pass into an apathetic mental state, losing interest in life, others have a definite residium loss of sexual appetite, their wifely and maternal instincts disappearing. The opposite is not unknown, and sometimes the sexual demands of these patients become excessive (Bompiani,[16] Strecker and Willey,[107] Pitimada[86]); this, however, is relatively uncommon. It is of interest that the male not infrequently becomes impotent as a result of the disease. The position of woman in this connexion is obviously different from that of the man, and provided her mental condition is not such as to render futile any advances of her mate, or her bodily state such as to render intercourse impossible (e.g. marked lower limb rigidity), there is nothing to prevent her conceiving.

Treatment.

The conclusions arrived at in the preceding pages must be carefully remembered when considering the treatment. Briefly they were these:—

1. Parkinsonism is liable to make its first appearance during or after pregnancy.

2. Parkinsonism frequently undergoes aggravation as a result

of pregnancy, the aggravation taking place most commonly either early in gestation, or shortly after the confinement.

3. Parkinsonism does not cause sterility.

Pregnancy, labour and the puerperium are usually adversely influenced by Parkinsonism.

5. The children are almost always healthy at birth, and apparently survive to live normal lives.

Prophylactic treatment.

The evidence is sufficient warrant for this title. The onset and aggravation during pregnancy are sufficiently frequent to demand the prevention of child-bearing in women who have recovered from the acute attack. This is, of course, a general statement and, like all such, must not be pushed to extremes. The rational course would be to advise women, on recovery from acute epidemic encephalitis, to avail themselves of precautionary measures against future pregnancies for a period. The length of that period must be determined by the subsequent course of events. Should no Parkinsonian symptoms appear during the ensuing four years it would appear justifiable to allow conception to occur. If, on the other hand, the slightest symptom appear during that time it would be wise to prolong the period of prohibition indefinitely, or until four years after the last symptom disappeared. To go further does not seem necessary. Those who are to become Parkinsonian do so, in the overwhelmingly large majority of cases, long before the elapse of four years; to taboo child-bearing in a healthy young woman for longer would be wrong.

Patients seen for the first time as Parkinsonians should be tendered similar advice, if anything, more strongly since aggravation appears to be more common than onset during pregnancy.

The advisability of sterilizing patients in either of the above groups can only arise in very special circumstances. It would be absolutely unjustifiable to sterilize a woman after an acute attack on the off chance of later development of residua. Such patients are too often young females who in the future will be desirous of becoming mothers, and there is always a reasonable hope that recovery will remain complete even though the acute phase coincided with pregnancy. Furthermore, sterilization is not a procedure lightly to be undertaken either on ethical or material grounds. The ethical side is referred to above, the material has reference to the risk attending any operation involving abdominal section. The scientific use of proper contraceptive measures, carefully explained by a competent medical adviser, should never act in a manner harmful to the patient.

The exception to this rule would be the case of a Parkinsonian patient who has had children, and whose abdomen had to be opened for some other condition; sterilization in this event would be advisable. It was practised by Strecker and Willey[107] in one case, ventral fixation being performed at the same time.

Treatment during Pregnancy.

Parkinsonism requires treatment whether the patient is pregnant or not. This, however, is the peculiar concern of the physician, and it would be out of place here to enter into a discussion of this highy controversial medical question. As in the case of acute epidemic encephalitis, the sole concern of the obstetrician has relation to the advisability or otherwise of interfering with the course of the pregnancy, and if interference is thought to be indicated the most suitable means to be employed.

The cases may be conveniently divided into the three following groups :—

(i) Those women who are Parkinsonian before becoming pregnant.

(ii) Those women in whom the onset of Parkinsonism coincides with the occurrence of pregnancy.

(iii) Those women who become pregnant after an acute attack but up to the time of being seen have not exhibited Parkinsonian symptoms.

(i) *Those women who are Parkinsonian before becoming pregnant.*

Because of the aggravation to which Parkinsonian patients appear to be prone during gestation, it would seem expedient, on theoretical grounds alone, to advise in favour of terminating these pregnancies. For the justification of this dogma it would be desirable to show that induction has been followed by an amelioration of the patient's condition, or at least that after the uterus had been emptied the symptoms became no worse; failing even this it would, of course, always be argued that if recourse had not been had to active measures the disease would have progressed still more rapidly in any given case. It is, unfortunately, not possible to say whether or no these desiderata are fulfilled; surprising as it may seem, in only two cases of Parkinsonism with pregnancy has induction been practised, at least so far as the published reports tell. These cases were recorded by Bompiani[16] in 1924; the first he terminated at the third month, taking as his indications aggravated nervous phenomena in association with mild toxæmia as evidenced by the presence of slight albuminuria with casts. He was unable

to observe any change in symptoms afterwards. He determined to induce premature labour in his other case, but at the moment of interference she went into labour (seventh month) thereby rendering induction unnecessary. Here again Bompiani's[16] indication was toxæmia with Parkinsonism. It has already been pointed out that following delivery the nervous symptoms became worse although those attributable to the toxæmia disappeared. It is thus clear that positive evidence in favour of induction in these cases cannot be adduced. In its absence it is necessary to fall back on the second line, furnished by those cases in which miscarriage, as opposed to labour at full time, has occurred. These too are scarce enough. If it could be shown that miscarriage, particularly in the early months, was either followed by improvement or not followed by the usual aggravation, then a hint on the question of induction would be obtained. But here again something in the nature of an *impasse* is reached because premature labour near term has been shown to be very much commoner than miscarriage during the early months; besides which where premature labour has been the rule the cases have been of more than ordinary severity. Certainly they have continued without exception their downhill course, and it is possible that induction late in pregnancy might be followed by a like result. On the other hand, it could be argued that but for the premature onset of labour these cases would have become worse with still greater rapidity, Nature herself guarding against this in her own peculiar way. Why not, therefore, imitate Nature by initiating in one or another way uterine contractions? If this was done, it might be said that in cases of less severity, improvement rather than aggravation would follow delivery, or at least there would be a surety of no exacerbation. Returning to miscarriage during the early months, Bompiani[16] recorded two cases in which subsequent to an acute attack of epidemic encephalitis, more than one miscarriage during the first three months of pregnancy occurred without any change in symptoms. Later pregnancies going to term caused accentuation of Parkinsonian symptoms. A similar case is reported by Fort.[37] Bompiani[16] asserts that miscarriage as opposed to full time labour does not adversely influence Parkinsonism. From this it might be deduced that induction early in pregnancy would be beneficial in preventing aggravation, but it cannot be denied that these pregnancies might not have aggravated the disease if they had continued. But since exacerbation is admittedly common during the early months it seems at least possible that interruption, natural or artificial, early in gestation has a favourable effect.

The position is exceedingly unsatisfactory and thus it will have to be left until such time as more evidence is available; in

the meanwhile the best line to take in these cases is to do nothing unless the symptoms begin to become more marked. Any accentuation should be carefully watched for during the first half of gestation, and, since such early aggravation is often followed by a more severe exacerbation early in the puerperium, it would probably be wiser to terminate pregnancy in the hope of averting later catastrophe, than to continue a policy of "wait and see' until the patient's condition becomes hopeless. This amounts to advising interference at the slightest provocation and, as such, may appear drastic, but it is to be remembered that Parkinsonism is a terrible infirmity and is known often to be made worse by pregnancy; induction is, therefore, justifiable if used only experimentally, until some effective therapeutic measure or measures are found for Parkinsonism itself or until obstetrical interference is shown to be of no avail.

(ii) *Those women in whom the onset of Parkinsonism coincides with the occurrence of pregnancy.*

Arguing on the same lines it would seem advisable to induce labour in these patients as soon as the Parkinsonism declares itself. By so doing, further aggravation such as occurred in Berkeley's and Cockayne's case, in Meyer's[74] case and in Fort's[37] two cases may be avoided. That such aggravation does not always follow is admitted, and that benefit will result from induction is by no means certain, but since aggravation is more than a possibility once Parkinsonism has become established, and since that aggravation is presumably caused by the pregnancy, it seems only logical to conclude that termination would lessen the chance of subsequent untoward happenings.

(iii) *Those women who become pregnant after an acute attack, but up to the time of being seen have not exhibited Parkinsonian symptoms.*

Clearly this group is in rather a different category from the other two. In them there was definite evidence of the activity of the virus, while in this group the virus is presumably inactive, whether finally exterminated or merely lying dormant, awaiting its chance, nobody knows. The lack of knowledge prohibits the adoption of active obstetrical treatment, but every care should be bestowed on the patients to enable them the better to go through pregnancy safely. They should be seen at frequent intervals, every precaution against over-exertion, and in general, such measures as will keep their health up to scratch should be taken. It would be wise to warn their relatives of the possibility of trouble, which is particularly liable to occur just after their confinement.

(c) *Treatment during Labour.*

Labour has been shown to present no very unusual features in the Parkinsonian, its conduct, therefore, requires but brief consideration. Labour in any woman with a disease which has caused severe bodily and mental derangement must necessarily be regarded as making a serious call upon her resources. The fact that these patients stand labour well does not necessarily mean that it is without harmful effects, on the contrary the frequency with which the disease becomes worse during the puerperium shows that labour is not without its influence, being probably one of several factors which combine to make the lot of the sufferer harder Therefore, these women should not be left long in the second stage without assistance by the forceps. The observation that sometimes the forces are inadequate forms an additional argument in support of the statement that labour is not so harmless as it seems, and furnishes a definite indication for instrumental delivery. The general line to be adopted, then, is one which will reduce the effort required of the patient to a minimum. It is well to remember that forceps-delivery may not be without difficulty in some of the cases, d'Andrea[4] finding the application by no means easy in his case, owing to extreme lower limb rigidity.

Treatment during the Puerperium.

The only question arising during the puerperium is that relative to lactation. Should these women be allowed to suckle their children? So far as the child is concerned the answer is in the affirmative, there being no authenticated case in which transmission by the mother's milk has occurred. In case 12 the child was suckled for nearly 18 months and was, in addition, subjected to a more or less continuous stream of saliva, a secretion known to carry with it the virus of the disease, yet the infant remained healthy.

The only consideration is, therefore, the mother. In the more marked cases there can be only one answer to the question—emphatically No. del Sole[109] insists on this, and it must be obvious that in cases so severe as his own he is right. The milder cases afford a different problem, and it may well be that lactation does no harm. On the other hand, by allowing it to continue, yet another call is made on the mother which may help to determine a change for the worse. The prohibition of suckling ought surely to be insisted upon because it can never be foretold what course a case is going to take. By attention to matters of this sort it may be possible in the future to abolish or diminish the puerperal aggravation.

Summary and Conclusions.

Prophylactic Treatment.

Because Parkinsonism not infrequently makes its first appearance with pregnancy and is, when already present, often aggravated by pregnancy, patients who recover from acute epidemic encephalitis should be advised not to allow themselves to become pregnant until after the elapse of four years from recovery. Similar advice should be tendered to those who are first seen as Parkinsonians.

If abdominal section be rendered necessary to a Parkinsonian woman with children sterilization should at the same time be practised.

Treatment during pregnancy.

(a) *Those women who are Parkinsonian before becoming pregnant.*

The question of terminating pregnancy is considered and the conclusion arrived at that the best line to take in this group of cases is one which involves very careful observation of the patients throughout pregnancy with active interference at the slightest provocation.

(b) *Those women in whom the onset of Parkinsonism coincides with the occurrence of pregnancy.*

The fact that Parkinsonian symptoms appear for the first time with pregnancy makes it advisable to induce labour in this group of cases.

(c) *Those women who become pregnant after an acute attack, but up to the time of being seen have not exhibited Parkinsonian manifestations.*

Patients in this group should be carefully watched throughout pregnancy and active treatment considered if any early signs of Parkinsonism appear.

Treatment during labour.

The course of labour should be rendered as easy as possible by shortening the second stage by the use of the forceps. Lower limb rigidity may interfere with its application.

Treatment during the puerperium.

Because aggravation of the disease is of common occurrence after the confinement, the strain of lactation should be avoided and the children fed artificially.

DETAILS OF CASES.

Case 1.

Professor Arthur J. Hall's Cases.

Mrs. C—, confined October 1924, at term, child normal.

Weakness of right arm first noticed during puerperium. It has got worse since. There is no history of the primary attack, but her friends had noticed slowness of movement before her confinement. There is now some sialorrhœa and facial mask. Right hand worse than left. Some tremor in both. Walks slowly.

It seems probable that the acute attack occurred during the prevalence of the epidemic in the spring of 1924, when she was in the early months of pregnancy, and that it was of so mild a character that it was not recognised as an illness. This is by no means an uncommon occurrence in the Parkinsonian cases.

Case 2.

Mrs. Cl—, 24. The acute attack began in March 1924, with severe headache and delirium. This lasted for one week and was followed by "trances." She was about four months pregnant. The acute attack lasted altogether for 10 or 12 weeks, with extreme lethargy, twitchings of the arms and legs, katatonia, ptosis and nystagmus.

She was confined in August 1924—a healthy full-time child. When seen in November 1924, she had become slow in her movements. The facies was typical and the left arm was chiefly affected. She had been unable to do anything for her child.

Her condition advanced rapidly and she died in January 1926.

Case 3.

Mrs. Co—, 32. Married December 1923. On February 16th, 1924 she had an acute attack of encephalitis—diplopia, delirium, extreme lethargy, severe cough. A normal child was born on October 25th, 1924, so that she must have been in the first month of pregnancy when infected. She suckled the child for five months. During the pregnancy she had attacks of polypnœa which would last a few minutes, also some sialorrhœa, but these seemed to improve Two weeks after her confinement she became worse. The breathing attacks were more severe, there was also constant twitching of the toes of both feet. She slept a great deal. The left arm also became stiff and felt weak. In the summer of 1925 shaking was noticed and she became much slower in everything. In January 1926, she was unable to wash or dress herself. The facies was definite but slight; no ocular symptoms. Stiffness and tremor in left arm and leg. Pains in tips of toes. This patient had lost two stones in weight.

Case 4.

Mrs. D—, aet (?), began with epidemic encephalitis in December 1920, while pregnant. Lethargy was a marked feature and hiccough was very obstinate. She was admitted to the Jessop Hospital for Women, Sheffield, and Cæsarean section was performed. The child was born alive and kept apart from its mother for the first six or seven weeks of its life. At that time the mother was discharged to her home and the child sent away to be nursed for four months longer. The mother was in bed until March 1921. After that she was unable, for some time, to walk about, owing to weakness

and loss of use in the legs. She gradually regained power. At the present time she shows a typical fixed expression, head immobile and has the usual quick speech. She complains of pains in the legs and hips, also across the forehead. She says her sight is hazy and that she sees things double when they are near. There is slight nystagmus, no squint, the pupils react normally to light and on accommodation, and the eyes converge normally. There is definite rigidity and slowness about the left arm and leg. The posture of the arm is characteristic and she complains of inability to use it freely. Thus she states that in attempting to peel potatoes the left hand will not keep up its time in manipulating the potato. Mentally she seems clear and up to standard.

I saw the child on December 30th 1922. She was then two years old. About two months ago the left arm "went loose"; the use was lost for about a day. It then recovered. A month later after being washed she fell over when standing up. The left leg was found to move queerly. Before this, she could walk three or four yards by herself, but since then she cannot take a step by herself, but has to hold on to something. They think she is improving. The left foot is colder than the right. The knee jerks are present on both sides, but the plantar response is less on the left than the right.

CASE 5.

Mrs. F—, 20, began in February 1924 by being very talkative and excited; she talked all day and night—rambled at times. She was then in the third month of her second pregnancy. A normal child was born at full time. Since this illness she has not been able to do her housework, but could wash and feed herself.

She became pregnant again and was confined of another normal full time child in September 1925. Since then she has been much worse. She can feed herself, but cannot wash or dress herself. She presents all the typical characteristics of well marked Parkinsonism. The right arm is more affected than the left.

CASE 6.

Mrs. Fl—, 21. Had acute encephalitis in February 1924, when three months pregnant and was an in-patient at the Royal Infirmary under Dr. Yates up to the time of her confinement on August 9th, 1924. The child was healthy. When I saw her in November 1925, she had been getting slower for about two months. She was then definitely Parkinsonian with marked sialorrhœa. The child died at the end of 1926, from what cause I could not ascertain. Since its death she has got much worse, and in March 1927, when I saw her again, she was quite unable to attend to herself, with extreme salivation and generalized advanced Parkinsonism.

CASE 7.

Mrs. Fr—, 25, married 4 years. In March 1924 she began with insomnia and visual hallucinations for two days. This was followed by diplopia and lethargy. She was in bed for three days because the use went out of her limbs. She was then three months pregnant. She says that for the rest of the pregnancy everything seemed strange and far off. She dare not cross the road because the traffic, though near, seemed far off. A healthy child was born at term. (She suckled the child for two months). Since then she has changed completely in character. She has no interest in her

child or in anything else. When I saw her in April 1925, she was a typical generalized Parkinsonian. Since then she had been getting steadily worse.

CASE 8.

Mrs. Fu—, 37, was admitted to the Jessop Hospital for Women on August 31st, 1922 on account of vomiting. She was then six months pregnant, this being her tenth pregnancy. She seemed dull and apathetic, but had no headache. On September 22nd some nystagmus was noticed, and she seemed confused. The vomiting was again troublesome. On October 15th there was diplopia and she had a fit. She was also drowsy and lethargic. Cæsarean section was done next day and a normal child removed. On the 22nd there were ptosis, nystagmus, fixed pupils, and jerkings in the left arm and leg.

CASE 9.

Mrs. Fur—, 24. The acute attack began on May 3rd, 1924, when in the last week of pregnancy. She had a terrible headache, lost her speech entirely, and partial use of hands. She could understand all that was said to her. Speech returned to a certain extent in a few hours. After a night's rest she seemed better, but was very drowsy. She was confined on May 11th. The child was quite healthy. Since then she has changed entirely in temperament. She is irritable, emotional and depressed.

In September she complained of pain in the right leg, weakness of right arm and leg. There is stiffness and loss of swing in the right arm; the right leg drags. The facial mask is not very marked; slight sialorrhœa.

CASE 10.

Mrs. J—, 25. Married August 1923. Acute encephalitis began in April 1924, with severe delirium, headache, diplopia and lethargy. She was then eight months pregnant and was confined on May 25th, 1924. The child was healthy in every way, and has remained so. After the confinement she never recovered her health, and apparently the symptoms of Parkinsonism came on early. This continued to get worse, the salivation being exceedingly troublesome. The arms have never been affected, according to her own statement, but apparently she was unable to do her housework or to get about. I did not see this woman until October, 1926, but I had heard about her from her medical attendant, Dr. Hudson, because of the surprising improvement which followed the administration of belladonna, early in 1926.

The interesting point in her case is, that even now in May 1927, although definitely Parkinsonian, she remains very much better than she was until she began taking belladonna. The salivation is not troublesome at all. The facies is distinctly present, but not marked. Although she says that the arms are not affected, she has lost all swing in walking, she takes short stiff steps, and there is some hesitation in moving the right foot. She complains of severe pains in the back and legs, and nothing seems to give relief.

She is one of the few cases showing a peculiar "setting" of the teeth, associated with permanent retraction of the lips—giving the appearance like "Risus sardonicus."

CASE 11.

Mrs. K—, 23. Subject to minor epilepsy since the age of 17. Married Easter 1923. In March 1924, she had an acute attack of encephalitis with

diplopia, visual loss and delirium lasting for three weeks. She was very lethargic and would fall asleep anywhere. She was then five months pregnant, and the question of terminating the pregnancy was considered. She was therefore admitted to the Jessop Hospital, where I was asked to see her. It was agreed to allow the pregnancy to proceed, and she had a normal labour on July 30th, 1924. The child was healthy. After this she says she recovered. A second healthy child was born on May 1st, 1926. After this she became worse. Salivation, weakness of both hands, with typical posture, right and left. Facies well marked. Tremor of eyelids, lips and tongue. Gait not affected. She has put on three stones in weight since 1924. The attacks of minor epilepsy have become worse and in September 1926, in one of these, she accidentally dropped a saucepan of hot water on to her baby, which died as the result of scalds. The patient in 1927 is a well marked Parkinsonian.

CASE 12.

Mrs. L—, 27, began suddenly in April 1924 with polypnœa which lasted for three days. She was then five months pregnant with her second child. She had also marked insomnia. She was not laid up in bed at all. She was confined of a healthy child at full time in August, 1924 Since the child was born she has been getting steadily worse. She has become slower in everything. She suckled her child continuously up to seven weeks before I saw her in January, 1926—i.e., for nearly 18 months. For the last six months she has become much worse. There is extreme salivation and typical Parkinsonism generalized. She has lost all interest in everything and cannot do anything in the house.

It is interesting to note that the baby, though suckled and probably fouled with the mother's dribbling saliva, day after day, has shown no symptoms of the disease.

CASE 13.

Mrs. M—, 27, began with headache and shivering on April 20th, 1924, when eight months pregnant. She was admitted to Lodge Moor Hospital. She was then very drowsy and stuporose, with mask face, unequal pupils, slight pyrexia, and twitching of the hands and mouth.

She improved and was confined of a normal child on May 18th, 1924. She recovered completely, and her medical attendant, Dr. Gilmore, states that in June 1927, both mother and child are quite well.

CASE 14.

Mrs. N—, 23. This patient began suddenly in May 1924 with diplopia, turning up of the eyes, lethargy by day and insomnia by night. She was then seven months pregnant. A normal child was born at term.

The history of the immediate period is uncertain, but when I saw her in June 1926, she was a complete Parkinsonian. It is said that about a year before—that is in the summer of 1925—she lost the use of her right arm, and tremors began, while six months later the legs were affected and there was severe sialorrhœa.

When I saw her at Hospital in June 1926, in addition to the typical features of advanced Parkinsonism, she had attacks of spasmodic deviation upwards of the eyes, which sometimes lasted for hours. This, in my experience, is more common in women than in men, though it occurs in both. She was mentally very depressed and had contemplated suicide. She was thought to be again three months pregnant.

CASE 15.

Mrs. P—, ? age, began with delirium shortly before her confinement on May 14th, 1924. It was thought to be puerperal insanity, and she was therefore admitted to the Jessop Hospital for Women on May 19th. She then had delirium of the occupational type with myoclonus of the arms and legs, nystagmus, tremor of the tongue and lethargy. In May there was some right facial paralysis. In January 1926, both she and the child were quite well, except that she complained of being rather sleepy in the daytime and sleepless at night.

CASE 16.

Mrs. R—, 21. Married October 1923. Acute attack about the first week of April 1924. She was shivery and feverish, talking continuously all night. There were diplopia, extreme lethargy in the day time, and twitching of the face. She was then in the fifth month of her first pregnancy. About six weeks after the onset of the attack, choreiform movements of the left arm and leg began, accompanied by complete insomnia. This continued for some weeks. In July she improved somewhat, but could not use the left leg properly.

She was confined of a normal child at term on August 23rd, and was apparently no worse after this. I saw her in December 1924. She was then apathetic and had lost all interest in the child. There was definite sialorrhœa. The face was markedly greasy. She was constantly picking at her nails or nose. She was very depressed and complained of constantly "rhyming" everything that she heard spoken, or thought of. She is sleeping badly and is distinctly suicidal. The arms are not affected. The left ankle gives way and turns over when walking.

A week later she attempted suicide and had to be removed to an asylum, when she again tried to strangle herself. She improved somewhat while there.

CASE 17.

Mrs. T—, 23, had epidemic encephalitis in the spring of 1920. She was laid up for three weeks, and has but little recollection of anything during that time. She was then in the third month of her first pregnancy. A healthy full time child was born on November 19th, 1920. It was not suckled. She was able after this to do her housework and look after the child. In the summer of 1922 she again became pregnant, and soon after this she became much slower and definitely Parkinsonian. A second healthy child was born at term in February 1923. She was then rather slow, the left pupil was larger than the right, nystagmus to the left, frequent drooping of the left eyelid. Usually there was no convergence, but once or twice she pulled the right eye in slowly. The facial mask was very marked. Tremor of lips and tongue. Weakness of the right side of the face. Arms showed marked postural tone. There was katatonia. Walks with trunk bent forward. Turns with body first. Slight tremor of arm and leg.

In November 1924, she was pregnant again and threatened suicide. She was admitted into the Sheffield Royal Hospital in February 1925, when her condition was that of severe Parkinsonism. She was about five months pregnant. The child was born in April 1926. It only lived a few hours, but there is no information as to the cause of death. After this the woman became quite unable to help herself in any way. She was readmitted to Hospital on September 2nd, 1926, in this helpless condition. On September

25th hyoscine hydrobromide 1/200 grain was given by the mouth thrice daily with marked benefit. In the course of a week or two she was able to feed and wash herself and gradually made herself useful in the ward, carrying round tea to the others and much less tremulous than she was.

Her condition remained much the same until November, when she began to get more helpless and was very depressed. On November 10th, the dose of hyoscine was increased to grain 1/150 thrice daily. She then improved again and, when discharged in December 1925, was able to get about and help herself.

CASES 18.

Mrs. W—, 25, began on February 6th, 1924, with twitching of the arms, legs and back. It began in the right arm, then in the left, then in the left leg and finally in the right arm and abdomen.

She was admitted to the Royal Hospital on March 4th, as a case of chorea of pregnancy. She was four and a half months pregnant.

The movements were not those of chorea, but definite myoclonic spasms. In about a fortnight they ceased in the limbs, remaining only in the left lumbar and abdominal muscles. These myoclonic spasms were very painful. She was also very restless at night. A normal child was born at term.

I saw both mother and child in January 1926. Both were perfectly well. The myoclonus had entirely disappeared.

CASE 19.

Mr. Comyns Berkeley and Dr. Cockayne's Case.

Mrs. S—, aet 26. During the early months of her fifth pregnancy in the autumn of 1923 this patient had an attack of drowsiness and double vision, lasting about a couple of weeks. She did not consult a doctor nor take to her bed. The pregnancy went to term and a healthy male child was born in March 1924. The baby was fed at the breast for nine months.

She again became pregnant in October 1925, soon after which she noticed a trembling in the right arm. She was admitted to the Middlesex Hospital on June 8th, 1926, with mask-like face and tremor of the right side, most marked in the right arm. She was delivered without difficulty at term of a healthy female child weighing eight and a half pounds. The confinement was normal; the presentation was a vertex, occiput anterior and to the right; the first stage of labour occupied 12 hours, the second ten minutes and the third ten minutes. She was discharged from hospital three weeks after delivery, the puerperium being uneventful. She suckled her infant for 12 months.

I, the author, saw this patient in December 1927, when she presented a typical picture of the Parkinsonian syndrome. Both she and her friends are convinced that she became considerably worse after discharge from hospital, and while suckling her baby. At the present time, she has marked rigidity of both right limbs, and continuous tremor of the right forearm, which is maintained in pronation. Her gait is characteristic, and she finds difficulty in bringing herself to rest. The facies is mask-like, almost continuous salivation causes her great distress. She is very emotional and bursts into tears without provocation. She is now quite incapable of doing anything for herself. Both children are healthy and of average intelligence for their age

CASE 20.

Mr. Victor Bonney's Case.

Aet. 30 years. The patient was attacked in 1924, during the fifth month of her fourth pregnancy, by diplopia and slight general symptoms thought to be of toxæmic origin. For this reason, Mr. Bonney was asked to see her about three weeks after onset. She was then suffering from diplopia, violent leg pains, mental irritability and lethargy of moderate degree. Because the urine was normal in quality and quantity toxæmia was excluded and a diagnosis of epidemic encephalitis made. After several consultations, it was decided to allow the pregnancy to proceed and confinement at term followed with delivery of a healthy baby of normal weight. Labour was practically painless. The patient made a slow recovery from her disease and even to-day is not quite normal mentally. She takes no interest in ordinary subjects, though can talk loquaciously and sensibly on matters in which she is interested, for example, education. Very marked prolapsus uteri followed the confinement and the perception of sensation disappeared from the external genitalia and contiguous parts. The child has remained healthy and intelligent.

CASE 21.

Mr. Comyns Berkeley and Dr. D. Evan Bedford's Case.

Mrs. D—. Shortly before her marriage in August 1925 this patient noticed a "trembling of the right hand" when at needlework. Previous to this she had been quite healthy, and can recall nothing suggestive of acute encephalitis. She became pregnant in November 1925, shortly after which the trembling became more marked. The confinement was expected on August 7th. Labour not having begun she was admitted to the Middlesex Hospital on the 15th. At that time she had deficient movement of the right arm. On August 23rd she went into labour after induction with castor oil and quinine. The duration of the three stages was 21¾ hours, 3½ hours, and 15 minutes respectively. The child was healthy in every particular. It was not suckled. Three weeks later she was discharged after an uneventful puerperium, there being no change in the Parkinsonian symptoms.

Her condition remained much about the same, though she lost her tremor, until the beginning of 1927, when she again became pregnant, and the trembling reappeared. Her mother, who has lived with her for a number of years, is convinced that after her second confinement in October 1927, the condition became worse. She was completely unable to do any needlework, was very slow, and at times troubled with salivation; the weakness in the right arm was more marked. At this time she occasionally had emotional outbursts. The baby was healthy and not fed at the breast.

In November 1927, she began to attend the out-patients department of the Middlesex Hospital under the care of Dr. Evan Bedford. She now has hypertonus and weakness of both right limbs. Her facies is slight but definite, with weakness on the right side. The deep reflexes are increased. On the whole, her condition is better than immediately after her confinement, though she is still unable to get about alone and is very slow. Both the children are quite well.

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