THE EFFECTS OF THE INJECTION OF NORMAL BRAIN EMULSION INTO RABBITS, WITH SPECIAL REFERENCE TO THE AETIOLOGY OF THE PARALYTIC ACCIDENTS OF ANTIRABIC TREATMENT.

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SURVEY OF THE LITERATURE.

THE occasional occurrence of "paralytic accidents" during the course of antirabic inoculation is well recognised as an unfortunate complication of that therapeutic measure. The cases have to be distinguished from the rare instances of paralytic rabies in which, usually after extensive bites from rabid wolves, the disease assumes an unusual form and in which the virus can be recovered from the central nervous system. The paralytic accidents on the other hand are in no way related to the date or severity of the original injury—on occasion the suspected animal has later been proved healthy—but are definitely associated in time with the commencement of the treatment; almost all occur within 7–23 days of the first inoculation, and fatal cases show no rabic virus in the nervous structures.

Simon (1913) collected all the cases recorded before the publication of his paper and gave an exhaustive literature. Schweinburg (1924) has recently described 35 cases with 8 deaths at the Vienna clinic. Stuart and Krikorian (1928) divide the cases in order of severity into three groups and quote Avezzu's figures (1923), based on an analysis of 140 cases, for their relative frequency and mortality. In the first place there occur mild localised paralyses referable to lesions of the peripheral nerves; these constitute 35 per cent. of the total and are not fatal. Cases of subacute dorso-lumbar myelitis account for 30 per cent., with a mortality of 5 per cent. The remaining 35 per cent. present the Landry syndrome and have the high death-rate of 30 per cent. None of the many modifications of the original Pasteur treatment are completely devoid of risk, although the incidence of accidents is far lower when carbolised vaccine is employed.

The histological lesions in fatal cases are often inadequately described, and as far as can be gathered of several types. Distinction has not, however, always been sufficiently sharply drawn between cases of true rabies arising during or after Pasteur inoculation and cases in which no rabies virus is present, at death, in the nervous system, and in which the lesions

are of a totally different order from those in rabies. Babes and Mironesco (1908) described oedematous swelling of the nerve fibres in the white matter with swelling and disappearance of axis cylinders; the vessels were surrounded by a wide embryonic zone of small elongated cells with oval, dark nuclei. In the grey matter the vessels showed similar changes with many leucocytes in the lumina; the nerve cells were atrophied and surrounded by an embryonic zone. This description suggests that the changes may well have been similar to those encountered in post-vaccinal encephalitis. In Jochmann's case (1913), the meninges over the lumbar cord were oedematous and the cervical cord showed a meningitis serosa circumscripta. The microscopical changes in the lumbar region consisted in oedema, necrosis of tissues immediately around the vessels and, in the grey matter, disappearance or degeneration of the large nerve cells with a scanty small-cell infiltration. The cervical cord was similarly but less markedly affected. Simon (1913) stated that the pathological findings consisted of an acute myelitis, particularly in the cervical cord, with a destruction of the white matter not seen in cases of rabies; Negri bodies were not present. The cord of Fielder's case (1916) showed acute softening, most marked in the cervical and least severe in the lumbar segments. Streaks of softening following more or less the lines of the septa (vessels) were accompanied by lymphocytic infiltration of the perivascular sheaths and polycellular infiltration in the surrounding nervous tissues. The illustrations appended to this article leave little doubt of the identity of the condition with the disseminated encephalomyelitis following vaccination, measles, smallpox, etc. Koritschoner and Schweinburg (1925) record the findings in the 8 fatal cases at the Vienna clinic as follows:

Case 1.   Haemorrhagic myelitis.

Case 2.   Disseminated myelitis of the posterior and lateral columns with destruction of the white matter in some areas.

Case 7.   Great congestion and oedema; in cord occasional perivascular and periganglionic infiltration.

Case 8.   (Reported separately by Adolf, 1924.) Transverse myelitis of 11th dorsal segment with tract degeneration above and below the lesion but no other pathological changes.

Case 31.   Very severe diffuse myelitis, particularly in the white matter, which in places was completely destroyed; marked infiltration of the grey matter.

Case 32.   Severe inflammation of the whole cord with intense polynuclear infiltration, oedema, congestion and haemorrhage. Everywhere the nervous structure was completely or nearly completely destroyed. Similar changes were present in the brain. Bacteriological examination was negative.

Case 34.   No autopsy.

Case 37.   Hyperaemia; no histological report.

Remlinger (1927), at the International Rabies Conference, could find little to say on the histological aspect of the cases of paralytic accident. Stuart and Krikorian (1928, 1930) state definitely that the fatal cases show perivascular cuffing with lymphocytes and plasma cells, and perivascular demyelination with disappearance of axis cylinders. In severe cases these areas coalesce and necrosis results. Bassoe and Grinker (1930) record a case in which the lesions were identical with those of the disseminated encephalomyelitis following vaccination, smallpox, etc.

The cause of these accidents is not yet satisfactorily determined. Although in individual cases (*e.g.* those of França, 1910 and Busson, 1926) the *virus fixe* has undoubtedly given rise to rabies in man, in the majority, in spite of the contentions of Koch (1912) who affirms the pathogenic rôle of the rabic virus and of Bassoe and Grinker who attribute the accidents to an attenuated virus, the bulk of the evidence is against the incrimination of the organism of rabies. Babes (1902), on the ground that rabid brain filtrates were toxic for rabbits while

normal brain filtrate was not, claimed that a hypothetical rabic toxin must be held to blame. The observation forming the basis of this assertion has not, however, been confirmed. Müller (1908) first suggested that the paralysis might be due to the toxic action of foreign nervous substance and researches stimulated by his supposition have afforded a certain amount of support for the hypothesis.

As long ago as 1898, Centanni found that rabbits tolerated injections of brain substance badly; the weakness, emaciation and abscess formation resulting were not due to infection at inoculation but to toxins produced by the decomposition of the injected material. Aujeszky (1900), while attempting to immunise dogs against rabies by the injection of normal nervous substance (10 c.c. of 1 in 11 ox-cord daily for 18 days), noted that some developed skin abscesses and became very thin and weak; convulsions and paralysis occasionally occurred. The experience of Heller and Bertarelli (1904) was similar, as was that of workers attempting to produce a neurolytic serum (Delezenne, 1900; Armand-Delille, 1906, etc.). More recently, Remlinger (1920) injected a rabbit with six graded doses, each of 20 c.c. and representing in all over 14 grm. of nervous material, of a 2–20 per cent. suspension of homologous brain. On the 55th day the animal developed complete paralysis of the hind limbs and died 3 days later; at autopsy congestion of the lumbar cord was noted, but no further examination was made. Remlinger and Bailly (1927) attempted to produce accidents in dogs by prolonged antirabic treatment (101 days). The liability to paralysis was not increased, though certain animals naturally predisposed might develop this complication. Harvey and Acton (1923) found that rabbits inoculated with homologous brain (1·6 grm. in 24 days) sometimes showed wasting of the muscles of the hind limbs followed by paraplegia and later by complete paralysis. Koritschoner and Schweinburg (1925) carried out an extensive series of experiments designed to imitate methods of treatment in current use. Using sterile human brain, they inoculated rabbits daily for 14 days with emulsions prepared according to the methods of Pasteur, Babes-Puscariu and Hoegyes; control animals were given similar emulsions of other viscera. Those treated with brain substance regularly lost weight, and a certain number developed flaccid paralysis which usually proved fatal; of those injected with emulsions of other tissues, only the muscle series showed similar changes. These results were most marked in rabbits treated by the Pasteur and Babes-Puscariu methods; with that of Hoegyes the animals remained almost normal or only lost weight slightly. The histological examination revealed hyperaemia and oedema of the spinal cord, degenerative changes in the nerve cells with neuronophagia, small haemorrhages affecting particularly the grey matter, and sometimes perivascular infiltration. Animals dying of other causes did not present similar lesions and no case of spontaneous paralysis occurred during the experimental period. The total amount of brain substance injected appears to have been small. They concluded that the foreign brain substance administered was responsible for the paralytic accidents in man. Quast and Licht (1926) have criticised this work and inquired whether the results might not have been due to the introduction with the inoculum of some other neurotropic virus; Cornwall and Beer (1926 b) thought that additional factors must have been at work to account for the high mortality. Inoculating rabbit or ox brain intraperitoneally or subdurally into rats, Miyagawa and Ishii (1926) claimed to have produced paralysis in from 70 to 100 per cent. of the animals in different experimental groups; histologically they found a large variety of cellular lesions in nervous and glial tissues. Here again it would seem that caution in accepting these results is necessary. More recently Schweinburg (1930) has modified his views and states that the harmlessness of the *virus fixe* can no longer be absolutely upheld; it is improbable that all cases of paralytic accident are due to the same cause, and in some at least the rabic organism is to be held responsible. Markowski and Legezynski (1929) have described paralysis in the dog during the course of antirabic injections; the cord of their animal showed a diffuse meningitis and acute myelitis. Cornwall and Beer (1926 a) pointed out that, according to

the method of treatment adopted, the average dose of brain substance injected into man is roughly between 0·046 and 0·0008 grm. per kg., or between 0·094 and 0·011 grm. per kg. if carbolised cord is used. Employing a carbolised emulsion, they gave several groups of rabbits' doses of monkey brain varying from 11 mg. per kg. in 14 days to 800 mg. per kg. in 20 days. One rabbit died suddenly for no apparent reason after its twelfth injection, a second became paralysed 18 days, and died 27 days after the conclusion of the experiment. They believed that phenol rendered the brain substance slightly less harmful, but in any case the toxic dose varied widely with the individual. Stuart and Krikorian (1928) demonstrated that, though it was possible to produce anaphylaxis in rabbits by the injection of foreign nerve substance, there was no relation between this and the paralytic accidents. Inoculating rabic, normal homologous and normal heterologous brain material in doses of from 0·28 to 1·12 grm. per kg. into rabbits, they concluded that fixed virus and rabic toxin had no etiological relation to the paralyses, which were due to some constituent of normal nervous tissue rendered inert by carbolising the inoculum. Within limits there was no connection between the apparent toxicity of this constituent (as evidenced by the occurrence of paralysis) and the dose of brain given. Individual predisposition on the part of the animal seemed to be an important factor. The symptoms were not due to the phenol which in the amounts administered had been shown to be innocuous. The cords of the animals suffering from paralysis were stated to be the seat of an acute myelitis, but no histological details were furnished.

Summarising the foregoing extracts from the literature, it may be stated that, after eliminating cases of true rabies, in some cases at least of paralysis arising during antirabic treatment, there have been found lesions very like those of the disseminated encephalomyelitis following vaccination, smallpox, measles, etc. The toxicity of brain material introduced parenterally into animals has been clearly demonstrated, and occasionally paralyses have occurred during the period of inoculation; the inference has been drawn that such paralyses are directly due to the nervous substance administered. Scant attention has, however, been paid to the histological aspect of the experimental results, and it is difficult to judge whether any lesions obtained are comparable with those in human cases. The relative frequency in recent years of disseminated encephalomyelitis as a sequel to certain exanthemata and the general resemblance of the lesions to those described from time to time in the paralytic accidents of antirabic therapy combine to make the investigation of this question a matter of the greatest importance.

Author's experimental work.

Rabbits were injected subcutaneously or intramuscularly with a suspension of brain tissue in normal saline. This was ordinarily prepared by grinding the sterile brain with quartz sand, under conditions as strictly aseptic as possible, until a perfectly homogeneous mass resulted; sufficient sterile sand to produce the required strength of suspension was then added with further grinding, the sand allowed to settle and the thick supernatant fluid decanted into small flasks to be kept at a temperature of − 10° C. until required. Since Aldershoff and Pondman (1928) have described peculiar symptoms in rabbits injected intracerebrally with an emulsion made by shaking the brain with glass beads,

it was thought possible that its properties might be modified by prolonged agitation and in some experiments resort was had to this mode of preparation.

In most cases the brains were perfectly fresh but the human brain used had undergone autolysis for about 24 hours in fairly warm weather. On commencing the trituration the brains were sterile, but during the grinding operations, occupying 10–15 minutes, on large amounts of tissue it was virtually impossible to avoid the risk of slight contamination from the air. Nevertheless, on culture the suspension was often proved to be sterile; in a few instances air cocci of a type studied by Fairbrother (1929) and considered by him to be non-pathogenic were obtained. In some instances the emulsion was heated for a variable time at 55° C.; in others, phenol was added in a concentration of 0·5 per cent. and the mixture incubated for 24 hours at 37° C. The animals were injected on 6 days each week or at weekly or irregular intervals. Because, in connection with post-vaccinal encephalitis, it has been suggested that vaccinia increases the susceptibility of the nervous system to noxious influences, some of the rabbits were vaccinated during the period of inoculations. Some died during the night and the remainder were killed when moribund; a full histological examination of the nervous system and other organs was undertaken. Weights were recorded at weekly intervals and the dosage set forth in the tables calculated on the average weight during the time of observation.

Before proceeding to a detailed account of the experiments, the general effects of the administration of foreign brain substance may be summarised. After a single large injection the animal becomes quiet and refuses food. On the second or third day the rectal temperature rises 2–3° F. and persists at the higher level for 1 or 2 days. The body weight falls considerably; thus an animal of 1500–2000 grm. may lose 150–200 grm. in a week, after which weight is slowly regained. With repeated smaller doses, the animal at first gains weight less rapidly than normal; it then begins to lose weight, becomes quiet and listless and finally dies, sometimes of an intercurrent infection, sometimes without obvious cause. At the site of inoculation the tissues quickly become indurated, and a rounded, fluctuating, encapsulated tumour, which may ultimately burst through the skin, is formed in the course of 10 or 12 days; these phenomena are much less marked when carbolised brain is employed. Various observers have stressed the frequency with which abscesses occur, but in the present work typical abscesses have been seen on very few occasions; the fluctuating swellings merely contain partly inspissated nervous substance in which, microscopically, the outlines of necrotic nerve cells and tissue elements can be distinguished. On culture, organisms of the type previously mentioned can be grown from their contents and this applies equally whether the emulsion introduced was bacteriologically sterile or not. In short, not only is it a matter of some difficulty to prepare an absolutely sterile emulsion, but it is also impossible to maintain the sterility of a large bulk of dead material after deposition in the tissues of the animal; in a personal communication Prof. Korenchevsky informed me that he had experienced the same difficulty when inoculating suspensions of other tissues. Partial calcification of the lumps may occur.

Experiments with guinea-pig brain.

Four rabbits were given graded doses of a 10 per cent. brain suspension heated for $1\frac{1}{2}$ hours at 55° C. and later of a 20 per cent. suspension heated for $\frac{3}{4}$ hour. The earlier doses were such as to correspond roughly with those of previous workers and when no results were obtained the amount administered was progressively raised. One rabbit was inoculated with a 25 per cent. unheated suspension. The animals marked with an asterisk were vaccinated with vaccine lymph on the 21st day of the experiment; the vaccination ran a normal course. The results are seen in Table I.

Table I.

Number	Inoculated	Total dose in grm. per kg.	Duration (days)	Result
R. 1*	Daily	17·5	30	Died
2*	,,	22·7	32	Losing weight; killed
3	,,	17·7	32	Losing weight; killed
4	,,	21·4	32	Losing weight; killed
16	Weekly	18·2	69	Alive and well

No case of paralysis occurred and histologically the central nervous system was normal. In some of the brains of both this and subsequent groups, Scharlach R sections showed numerous globules of neutral fat in the cells lining the choroid plexuses, but as these have also been seen in control animals the observation has no significance. The other organs were normal.

Experiments with sheep brain.

Five rabbits received successively 10 per cent. suspensions heated for $2\frac{1}{2}$, $1\frac{1}{2}$, and $\frac{1}{2}$ hour at 55° C. and later a 20 per cent. unheated suspension. The last was unfortunately contaminated and the three animals (6, 8, 9) surviving at this stage died of infection with *B. coli*. The dosage, etc., is recorded in Table II.

Table II.

Number	Inoculated	Total dose in grm. per kg.	Duration (days)	Result
R. 5	Daily	12·4	11	Died immediately after an injection
6	,,	9·2	15	Sepsis; died
7	,,	15·4	11	Moribund; killed
8	,,	15·8	14	Sepsis; killed
9	,,	19·9	15	Sepsis; killed

None of the animals developed paralysis and none showed lesions in the central nervous system. The other organs of R. 5 and R. 7 were normal; in the remaining animals focal necroses and early abscess formation were present in the various viscera.

Experiments with human brain.

Ten rabbits were given increasing amounts of a sterile unheated suspension of human brain (from a case of lymphadenoma). On the 14th day of the experiment R. 19 and R. 20 were inoculated intradermally with neurovaccine (0·2 c.c. of 5 per cent. emulsion); the usual severe reaction with vaccinial

nodules in the lung, etc., followed. Four rabbits (R. 32–35) were placed on much smaller doses; when after 14 days no very marked toxic effects were evident, the doses were slightly and progressively increased without, however, attaining the magnitude of those in the other series. The full details are recorded in Table III.

Table III.

Number	Inoculated	Total dose in grm. per kg.	Duration (days)	Result
R. 10	Daily	4·6	5	Died immediately after an inoculation
11	,,	17·6	19	Died
12	,,	10·7	10	Moribund; killed
13	,,	14·3	20	Moribund; killed
14	,,	15·4	20	Died
15	,,	42·3	44	Alive and well; killed
19*	,,	15·4	19	Paralysis 5 days; moribund; killed
20*	,,	15·7	17	Paralysis 3 days; moribund; killed
21	,,	4·7	7	Died immediately after an inoculation
22	,,	10·6	14	Moribund; killed
32	,,	5·6	52	Alive and well
33	,,	5·3	52	Alive and well
34	,,	6·9	52	Alive and well
35	,,	1·7	17	Died

* Vaccinated.

Five days before death, R. 19 developed considerable weakness of the left hindlimb; this progressed to complete paralysis involving both hindlimbs and the right forelimb. Three days before death, R. 20 showed similar paralysis of the right forelimb and the left hindlimb. Both animals quickly went downhill and were killed when moribund. In each case the brain together with the whole spinal cord was removed and sections taken from numerous levels; the histological appearances were everywhere quite normal. The peripheral nerves were not examined. This surprising result will be discussed later. In the other organs the lesions of generalised vaccinia were evident.

In the terminal stages several of the rabbits suffered from diarrhoea; cultures of the intestinal contents yielded no abnormal organisms and the blood was sterile.

In several cases sections from the various viscera were stained for fat with the following results. In the liver many of the Kupffer cells contained fine Scharlach-staining granules and the cells of some of the smallest bile ducts were similarly affected. Large patches of liver cells situated in the central or mid-zonal regions of the lobules were heavily infiltrated with fat in the form of coarse droplets while other areas were wholly free. In the kidney, fat was present in the cells of some convoluted tubules in the deeper parts of the medulla; here again a number of adjacent tubules were involved and the intervening areas spared. Large globules of fat occupied the lumina of some Henle and collecting tubules but the lining cells were normal. In the lung, fatty granules were found in leucocytes and in the cells of the alveolar walls but not in the alveolar epithelium; a few granules were situated in the cells of the lymphoid follicles. In the spleen, fat was present only in the peritoneal cells on the surface; in the brain, only in the choroid plexuses.

R. 15, apparently well when killed, showed inflammatory foci in the lungs, patches of acute necrosis in the adrenals and large collections of polymorphs in the splenic pulp. The brain was the seat of a monocellular meningitis without deeper changes; no encephalitozoa or other parasites were demonstrable. Identical appearances were seen in an apparently healthy control for this series of animals.

In R. 22 an organising thrombus filled the lumen of a large branch of the right pulmonary artery and certain changes were noted in the area of lung supplied by this vessel. The portal tracts of the liver were densely infiltrated with lymphocytes and plasma cells.

With these exceptions, no abnormalities were detected in the central nervous system or other organs of this series of animals.

Experiments with monkey brain.

Two rabbits (R. 17 and 18) were inoculated with a 25 per cent. unheated suspension of monkey brain. Nine animals (R. 23–31) received a 10 or 15 per cent. emulsion prepared by shaking the brain and requisite amount of saline with a large number of glass beads for 4 or 5 hours. Four animals (R. 36–39) were given much smaller doses, roughly analogous at first to those used by Stuart and Krikorian (1928) and only increased later when no results were obtained. Finally, four (R. 40–43) received similar doses of a carbolised brain emulsion. The results are recorded in Table IV.

Table IV.

Number	Inoculated	Total dose in grm. per kg.	Duration (days)	Result
R. 17	Weekly	16·3	43	Moribund; killed
18	,,	14·8	48	Moribund; killed
23	Daily	16·5	49	Died
24	,,	9·9	11	Died
25	,,	8·4	14	Moribund; killed
26	,,	10·0	11	Died
27	Irregularly	6·3	11	Weakness right side 3 days; moribund; killed
28	,,	7·4	19	Moribund; killed
29	,,	4·5	12	Paralysis 2 days; moribund; killed
30	,,	12·5	35	Moribund; killed
31	,,	5·0	13	Died
36	Daily	6·9	68	Alive and well
37	,,	4·6	35	Died immediately after an inoculation
38	,,	0·4	6	Died of sepsis from wounds caused by fighting
39	,,	6·7	68	Alive and well
40	,,	4·2	43	Moribund; killed
41	,,	8·3	68	Alive and well
42	,,	1·2	16	Died
43	,,	1·8	16	Died

R. 27 developed well-marked weakness of the right fore- and hind-limb 3 days before its death and R. 29 complete paralysis of the hind-limbs 2 days before. In neither case was there any lesion in the brain or at many levels of the spinal cord; examination of the peripheral nerves yielded entirely negative results.

As before, several of the animals suffered from severe diarrhoea in the terminal stages.

R. 18 showed areas of necrosis in the liver and spleen, R. 27 in the liver and R. 31 in the liver, spleen, adrenal and lung. In R. 42 inflammatory nodules in the lung contained an aspergillus-like fungus; similar granulomata without detectable organisms were situated in the liver, and areas of acute necrosis in the adrenals. A mononuclear meningitis was present in the central nervous systems of R. 42 and 43 and also in an apparently healthy control; no parasites were visible.

Several animals dying without paralysis during the Christmas holiday presented necrotic

areas in the liver, spleen or lung but were not investigated microscopically. R. 40 (carbolised brain) died with an empyema. In no cases other than those described above were lesions found in the central nervous system.

SUMMARY.

In the experimental work just detailed, rabbits have been inoculated with suspensions of foreign brain material of guinea-pig, sheep, human and monkey origin; these have either been untreated or modified by the action of moderate heat or by the addition of carbolic acid. The dosage has varied within wide limits, sometimes approximating at first to that employed by other recent workers and increased later when no results had been obtained, at other times far exceeding that in most previous investigations. With comparatively small doses the animals have often, in spite of some loss in weight, remained alive and well for as long as 68 days. With larger doses a considerable loss of weight has perhaps been accompanied by severe diarrhoea and death has almost invariably ensued; such cases can be considered under three headings.

1. *Animals dying of an obvious infection.* Apart from the occurrence in the sheep-brain series of sepsis from a contaminated inoculum, a certain number of rabbits have shown lesions in the internal organs suggesting a terminal acute infective process; a few have been affected by diseases probably ante-dating the experimental period. The former infections have not been associated with obvious sepsis at the site of inoculation, though the presence there of certain organisms has already been mentioned; on one occasion a coccus of this type was isolated at death from the blood stream and injected in large quantities into the veins of a healthy rabbit without untoward result (Dr R. W. Fairbrother). Although Susman (1927) has shown that the effect of a watery brain extract prepared by boiling is to augment greatly the resistance of animals to various infections, the conditions of his experiments were totally different from those obtaining in the present work. There seemed every reason to expect that a proportion of the animals in an emaciated and toxic state, resulting from the autolysis or absorption of large volumes of foreign nervous tissue, would lose their natural resistance to pathogenic organisms latent in their bodies or acquired during the course of the experiments. In three rabbits a monocellular meningitis, associated in two cases with visceral lesions, was seen in the central nervous system, but the discovery of identical changes in two apparently healthy controls robs this observation of any significance.

2. *Animals dying without any important microscopical lesions.* Most of the fatal cases fall into this category. Attention has been drawn to the accumulation of moderate quantities of fat in various situations, and in the present group this has represented the sum total of the pathological changes detected. In these cases no satisfactory explanation of the fatal result other than the existence of an intense toxaemia can be advanced. It will be noted that three rabbits died immediately after an inoculation, and in none of these was a satisfactory explanation of the sudden ending forthcoming; Cornwall and Beer made a similar observation in their investigation.

3. *Animals dying with paralysis.* Only four rabbits, *i.e.* under 10 per cent. of the total, developed symptoms referable to disturbance of the nervous functions. All were receiving very large doses of brain matter and two had in addition been vaccinated with neurovaccine. In two a very full examination of the brain and spinal cord was made, and in two the investigation covered also the peripheral nerves. The astonishing outcome was that no lesions of any degree could be found; in every case the vertebral column was normal and despite the most diligent search no cause for a paralysis, in one instance preceding death by 5 days, could be determined. It so happened that about this time Dr Petrie of the Lister Institute Serum Department, Elstree, kindly forwarded the brains and cords (*in situ*) of two rabbits which, in the course of experiments with haemolytic sera, developed precisely similar symptoms and were killed after 9 days. Again, a very careful examination of the bones and of the central nervous system revealed no condition capable of accounting for the paralysis. From this experience, however, it seems extremely improbable that in our own cases the nervous trouble was directly attributable to the brain substance injected.

DISCUSSION.

The consideration of these findings affords definite confirmation of the alleged toxicity of normal brain substance, as manifested by the wasting and death which follows the inoculation of brain emulsions into animals. It also appears that in a small percentage of cases paralyses may develop during the period of inoculation; various observers have claimed that these are analogous to the paralytic accidents of antirabic treatment and attribute both to the foreign brain introduced. The present work shows that this assumption must be accepted with reserve for, as we have seen, precisely similar paralyses have occurred in the course of other work in which brain substance was not employed. It is true that we are in the unsatisfactory position of being unable, in either set of experiments, to explain the reason for the paralysis or to indicate its cause, but the fact that no lesions are discoverable in the central nervous system at once distinguishes the experimental condition from many of the cases of paralytic accident, in which lesions of a very definite nature have been described. It is unfortunate that the majority of observers who, by the above means, have produced paralysis in animals make no reference to the histological findings. Stuart and Krikorian state that the cords of their rabbits were the seat of an acute myelitis but do not mention whether this diagnosis was founded on macroscopical or microscopical appearances or, if the latter, what exactly were the characters of the inflammation. Koritschoner and Schweinburg and Miyagawa and Ishii alone appear to have made a careful histological study of a number of cases and the lesions they describe do not tally with those recorded in man by Babes and Mironesco, Fielder, etc. Now, as pointed out in the introduction, there are good grounds for believing that in many cases the human lesions are identical with those of the disseminated

encephalomyelitis following the exanthemata, in which event it can hardly be held that the brain injections (or, as the case may be, the viruses of vaccinia, etc.) do more than stimulate into activity some latent factor or factors which are truly responsible for the nervous disability. Even if, as statistical evidence seems to show, paralytic accidents are a function of the quantity of brain substance administered, this may only mean that the activation of the second factor is favoured by a greater degree of toxaemia. It is, therefore, maintained that the view postulating the identity of the paralyses in animals following the injection of brain substance with the paralytic accidents in man is based largely on clinical data, notoriously unreliable in dealing with so common a symptom, and that it is not warranted by the histological evidence so far available.

CONCLUSIONS.

The introduction parenterally in rabbits of emulsions of normal brain tissue is followed by severe toxic manifestations leading to wasting and death.

In a few cases paralyses occur, but similar nervous symptoms have been encountered in other work not involving the use of brain emulsions; the cause of these paralyses has not been determined and histologically no lesions in the central or peripheral nervous system have been detected.

There is insufficient evidence to warrant the view that the paralytic accidents of antirabic treatment are directly due to the foreign nervous substances injected.

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