THE RAPID PRODUCTION OF ACUTE DISSEMINATED ENCEPHALOMYELITIS IN RHESUS MONKEYS BY INJECTION OF HETEROLOGOUS AND HOMOLOGOUS BRAIN TISSUE WITH ADJUVANTS*

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Plates 1 and 2

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Multiple lesions of the central nervous system characterized by their wide dissemination, predilection for the white matter, perivascular position, inflammation, proliferation of histiocytes, giant cell formation, and associated demyelination, have been produced in several laboratories by intramuscular injection into monkeys of emulsions and extracts of rabbit brain (1–3). The procedure, however, involved as many as 30 to 100 injections and intervals of 3 to 13 months were required before symptoms appeared. On the hypothesis that the lesions might result from the interaction between the brain tissue of the host and antibrain antibody formed to the injected material, it was considered of interest to study the effect of adjuvants on this process. Administration of a variety of antigens as an emulsion with aquaphor, paraffin oil, and killed tubercle bacilli as described by Freund and McDermott (4) has yielded an enhanced immune response with a number of other substances (4–13). It was found that the clinical and pathological picture of acute disseminated encephalomyelitis, similar to that previously reported (1–3) could be induced in a relatively short period by three injections of an emulsion of normal rabbit brain containing these adjuvants (14). At about the same time Morgan (15) independently reported similar findings in monkeys on injection of emulsions with adjuvants of normal monkey spinal cord. This communication and the accompanying one by Morgan (16) summarize the detailed results obtained by this technique in the two laboratories. In the present study it has been possible to induce disseminated encephalomyelitis with emulsions of adult rabbit or monkey brain containing adjuvants; negative results were obtained with similarly prepared emulsions of fetal rabbit brain or of rabbit lung tissue.

EXPERIMENTAL

Preparation of Emulsions.—The emulsions used for immunization were prepared under sterile conditions as follows: 7 to 9 gm. of freshly removed tissue were homogenized in a Waring blendor in 10 ml. of saline containing 1 per cent of phenol. 10 ml. of aquaphor, kept at the

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lowest temperature at which it would remain liquid, were added and homogenized with the tissue suspension. To this mixture were added 20 ml. of paraffin oil in which 25 mg. of heat-killed dried tubercle bacilli had been uniformly suspended and the mixture agitated until an emulsion of uniform consistency was produced. It was transferred to sterile bottles, sealed with rubber caps, and heated at 60° C. for 45 minutes to destroy autolytic enzymes. Each milliliter of the final emulsion was equivalent to about 175 to 225 mg. of original tissue; the medium contained a final concentration of 0.25 per cent phenol. Emulsions of adult and fetal rabbit brain, rabbit lung, adult monkey brain, monkey grey matter, and monkey white matter were used. All materials were prepared as described above or in multiples of these amounts, except that 13 gm. of rabbit lung and in one instance 3.9 gm. of fetal rabbit brain were used instead of the 7 to 9 gm. specified above. In the case of this fetal rabbit brain emulsion the amount injected was increased by 50 per cent to compensate for the smaller amount of tissue per milliliter of solution. The fetal rabbit brain was obtained from 6 litters of fetuses; only the cerebrum was used. From each litter of fetuses of which two were 4 cm. in length, two 5.5, one 6.5, and one 8 cm. in length, two individuals were set aside for histological examination. The brains were fixed in 10 per cent formalin and stained for myelin sheaths by the Mahon stain. The cerebrum in each instance was free of myelin.

Injection of Animals.—In general, *rhesus* monkeys were each given an initial series of three injections (first course) of 1 ml. of the emulsions prepared as above. Injections were spaced a week apart and were given intramuscularly. At the end of this period the animals were observed for 3 weeks to 1 month. Animals which showed no symptoms received a second course of inoculations of 1 ml. once a week. The injection schedules of the various groups of animals appear in Table I. One group of two animals each received a single injection of 2 ml. of rabbit brain emulsion.

In addition, a group of two monkeys each received a series of weekly intravenous injections of 5 ml. of serum from animals which had shown clinical symptoms after injection with adult rabbit brain emulsions, until a total of 35 and 40 ml. respectively had been given.

Monkeys were observed frequently for clinical signs of neurological disease and allowed to live until they no longer appeared likely to survive to the following day. They were then sacrificed by exsanguination. Blood and portions of brain were cultured aerobically and anaerobically and invariably were sterile. In several instances brain tissue was inoculated intracerebrally and intraperitoneally into several mice and into a rabbit and in one instance into a normal monkey; all animals remained healthy.

A complete autopsy was performed on each animal. The brain, spinal cord, peripheral nerves, eyes, and optic nerves were fixed in 10 per cent formalin for periods up to 3 weeks and then sectioned and stained by the usual neuropathological techniques. In some instances, fresh segments of brain were fixed in a solution of formalin and ammonium bromide or in 95 per cent alcohol or were refixed in Weigert's mordants and stained by appropriate methods. Samples of each of the remainder of the organs and tissues were fixed in Zenker's fluid, embedded in paraffin, and stained with hematoxylin-eosin and by other techniques.

RESULTS

In all, thirty young, healthy *Macacus rhesus* monkeys were inoculated intramuscularly with the various emulsions of tissue containing adjuvants, and two were injected intravenously with the sera of monkeys which had shown neurological symptoms. Nine of the thirty received adult rabbit brain, ten, adult monkey brain, seven, fetal rabbit brain, and four, rabbit lung. The number of inoculations that each monkey received, the time that elapsed

TABLE I

Effects of Injections of Rhesus Monkeys with Emulsions of Heterologous and Homologous Brain and Other Tissues Containing Adjuvants

Material injected	No. of monkeys used	First Course: No. of 1 ml. injections at weekly intervals	Monkey No.	Results: Day symptoms first noted after 1st injection	Clinical picture	Day of death	Necropsy findings	Second course: Day started	No. of monkeys	No. of injections at weekly intervals	Results: Day symptoms first noted	Clinical picture	Day of death	Necropsy findings
Adult rabbit brain	4	3	6	23	Ataxia; quadriplegia; left internal strabismus; ptosis, left eyelid	25(S)*	3+							
			5	30	Right hemiparesis; weakness, left lower extremity; myoclonic twitches	30(S)	2+							
			8	33	Ataxia; reduced vision; weakness, left upper extremity	40(S)	2+							
			7	Negative	No symptoms		0	40	1	4	No neurological symptoms		94(S)	0
Adult rabbit brain	3	3	11	17	Ataxia; vertical nystagmus; right internal strabismus; right lower facial weakness	18(S)	3+							
			9	20	Left internal strabismus; paralysis, left upper extremity, diminution of vision; vertical nystagmus; paresis, left lower extremity	24(S)	3+							
			10	30	Right internal strabismus; paresis, right arm; slight ataxia	31	3+							
Adult rabbit brain	2	1‡	13	22	Ataxia; strabismus; right hemiparesis; blindness. All remittent and recurrent	45(S)	2+							
			12	62	Left facial weakness; left hemiparesis; blindness, ataxia	67(S)	1+							
Adult monkey brain	4	3	19	0§	No neural symptoms. Sudden death	13	0							
			20	15	Right lower facial weakness; head tremor; ataxia; blindness; auditory hypersensitivity	27(S)	1+							
			22	30	Tremor of head and trunk; ataxia; left internal strabismus; diminution of vision, ptosis; left upper lid	51(S)	2+							
			21	32	Ataxia	32(S)	3+							

TABLE I—*Concluded*

Material injected	No. of monkeys used	First course: No. of 1 ml. injections at weekly intervals	First course: Monkey No.	Results: Day symptoms first noted after 1st injection	Results: Clinical picture	Results: Day of death	Results: Necropsy findings	Second course: Day started	Second course: No. of monkeys	Second course: No. of injections at weekly intervals	Results: Day symptoms first noted	Results: Clinical picture	Results: Day of death	Results: Necropsy findings
Adult monkey gray matter	3	3	26	32	Blindness; remittent and recurrent.	37	2+							
			27	33	Tremor hands and head; ataxia, blindness; intermittent vertical nystagmus	37(S)	2+							
			28	36	Left hemiplegia	51(S)	1+							
Adult monkey white matter	3	3	31	28	Ataxia	28(S)	2+							
			33	32	Tremor of hands and body. Ptosis of both eyelids; blindness; ataxia	37(S)	2+							
			32	32	Ataxia; tremor of extremities and trunk	47(S)	1+							
Fetal rabbit brain	3	3	16		No neurological symptoms			38	1	1	No neurological symptoms	All negative	40(S)	0
			17		All negative				1	2			49(S)	0
			18						1	3			69	0
Fetal rabbit brain	4	5	38		No neurological symptoms	76	0							
			39			33	0							
			40		All negative	76(S)	0							
			41			60(S)	0							
Adult rabbit lung	4	3	2		No neurological symptoms			35	4	5	No neurological symptoms	All negative	86	0
			4										87(S)	0
			3		All negative								94(S)	0
			1										98(S)	0

Necropsy findings:
1+ = mild lesions throughout CNS and/or few intense focal lesions.
2+ = moderate lesions throughout CNS and/or moderate numbers of scattered severe lesions.
3+ = severe lesions throughout CNS and/or few scattered very severe lesions.
0 = no lesions.
* S = sacrificed.
‡ 2.0 ml. of emulsion injected.
§ Found dead 5 days after second injection.

until the animal became ill, the nature of its symptoms and signs, and the intensity of the lesions in the central nervous system are detailed in Table I.

A single sample protocol is given:

Monkey 8—This animal was well and active when received on November 10, 1945, and was at once inoculated into the muscles and subcutaneous tissues of the lateral aspect of the right

thigh with 1.0 ml. of rabbit brain emulsion with adjuvants. On November 17th, a second injection was given into the lateral aspect of the right arm and on November 24th, a third was given into the right thigh. Tense swellings developed at the sites of inoculation and intermittently drained purulent material through small ulcerations in the skin which healed as the swellings receded. On December 13th, the animal was found to be very quiet and unsteady, and could not coordinate its movements well. On December 15th, the head was found rotated to the left and flexed forward. The pupils were widely dilated and when a hand or other object was thrust rapidly at the animal's eyes, there was no reaction, indicating a loss of vision. There was marked trunk ataxia; the animal squatted, hunched over, supporting itself by its forelimbs, and swayed violently. During the next 6 days the weakness in the left arm disappeared and a possible weakness developed in the left leg. The other signs persisted or progressed and the animal was sacrificed by exsanguination and chloroform inhalation on December 21st, 42 days after the first injection, 27 days after the last, and 6 days after the inception of symptoms. Aerobic and anaerobic blood cultures were negative. A sterile segment of the right parietal lobe of the cerebrum was ground up, suspended in physiological saline solution, and inoculated intracerebrally and intraperitoneally into one rabbit and three Swiss white mice with negative results. Postmortem examination revealed lesions confined almost entirely to the central nervous system and the local inoculation sites.

This protocol is quite typical. Variations occurred in the rapidity of development of symptoms and their duration (Table I). When the symptoms became so severe that it did not seem likely that a monkey would survive another day it was sacrificed. Of the nineteen monkeys receiving adult rabbit or adult monkey brain all but two became ill and showed lesions in the central nervous system. The eleven monkeys that received adult rabbit lung and fetal rabbit brain showed no symptoms or signs referable to the central nervous system nor were any lesions discovered in the brain or spinal cord postmortem. The two animals which had received injections of serum from animals which showed symptoms were observed for 62 and 83 days respectively. Both animals remained well and showed no gross lesions at autopsy other than mild pneumonyssus infestation of the lungs.

Spinal fluid was obtained from seven of the animals by lumbar or cisternal puncture. The results were as follows:—

Monkey No.	Total Protein	Leucocytes	Differential white count		Erythrocytes
			Polymorphonuclear neutrophiles	Lymphocytes	
		*per mm.*³	*per cent*	*per cent*	*per mm.*³
9	152	667	35	65	695
12	72	2			427
13	56	107	16	84	100
21	165	254	20	80	5000
22	52	18			
28	11				
33	110				

In six of seven instances elevations in the total protein and in four of the five animals examined an increased cell count with lymphocytes predominating were noted.

Description of Pathological Changes in the Nervous System[1]

Seventeen of the nineteen animals receiving adult brain inoculations showed abnormal changes in the central nervous system. Fifteen of these animals had gross lesions discernible only in the brain. For the most part these lesions were small and relatively inconspicuous, although occasionally large ones up to 2 cm. in diameter were encountered. They were most frequent in the subcortical and central white matter of the cerebrum but were found elsewhere in the brain as well. Although predominantly placed in white matter, they not infrequently extended into nearby grey matter and at times lay wholly within it. As examined in formalin-fixed slabs of brain, they were chiefly round, oval, or linear, greyish, greyish-pink, and yellowish-grey lesions that were indistinctly and less often sharply demarcated. Some were studded with petechiae, occasionally purely hemorrhagic foci were found, and in one instance this was of considerable size.

Histologically the fundamental type of lesion was found to be focal and related to a blood vessel: venule, vein, capillary, arteriole, and small artery, the first three being by far the most frequent in the order given (FIGS. 5–8). The abnormal changes were most frequent in the pons (FIG. 2), optic nerves (FIG. 4), and white matter of the cerebellum, although lesions were constant and common in the white matter of the cerebrum as well (Fig. 1). There was some tendency to periventricular disposition of the lesions and this was most striking about the fourth ventricle. The white matter of the brain was primarily involved with secondary or less intense, independent, abnormal changes in the grey matter. Lesions were scattered and infrequent in the spinal cord. In monkeys 26 and 28 the lesions were limited almost exclusively to the optic nerves and tracts and geniculate bodies.

In animals dying or sacrificed during the first few days after neurological symptoms were observed, the changes were acute. Polymorphonuclear neutrophiles, occasional eosinophiles, and sometimes fibrin were present in the walls of the vessels, their perivascular spaces, and in the perivascular parenchyma (FIG. 5). This infiltration was associated with congestion, edema, and occasionally fresh perivascular hemorrhages (Fig. 8). About these vessels there was myelin degeneration (Fig. 3) and often the perivascular zones of demyelination coalesced (Fig. 1). There was a relative preservation of the axones in these areas. Thrombi were rarely encountered in capillaries and small veins. These acute changes were encountered not only in animals succumbing rapidly,

[1] A more detailed description of the clinical and pathological findings will be published elsewhere.

but also in monkeys that survived longer and developed groups of new symptoms at intervals.

Those monkeys that lived beyond the 3rd or 4th day after the onset of their symptoms began to show a replacement of polymorphonuclear neutrophiles by lymphocytes and large mononuclear cells (Fig. 6). There was perivascular microglial proliferation and hypertrophy and less frequent early astrocytosis. As the process proceeded broad bands of large mononuclear cells having an epithelioid appearance were encountered perivascularly (Fig. 7) but no multinucleated giant cells were seen. In animals which survived longest, inflammation had receded or disappeared, demyelination was subsiding or complete, and microglial phagocytes were prominent. Astrocytosis was mild or moderate.

The findings in other organs and tissues were unrelated and often slight except for the florid local lesions in skin, subcutaneous tissue, and muscle at the sites of inoculation. These were composed of dense masses of epithelioid cells showing focal necroses and only occasional giant cells.

Pulmonary tuberculosis occurred in five monkeys, Nos. 3, 4, 7, 8, and 9, and was associated with multiple lesions in the liver and spleen in two of these animals. Pneumonyssus infestation of the lungs was very frequent in the entire series of monkeys occurring in at least fifteen, but for the most part it produced no serious symptoms or extensive lesions.

DISCUSSION

The etiology of the demyelinating diseases is as yet obscure. The considerable number of possible causative factors advanced and stoutly advocated serves to emphasize this. Infection, toxemia by endo- or exotoxins, the circulation of lipolytic substances, venous obstruction, and immune reactions or allergic manifestations have been proposed on the basis of clinical and pathological investigations (for a review *cf.* reference 17). The essential unity of the demyelinating diseases has been repeatedly suggested and an increasing body of clinical and pathological evidence would seem to lend this conception some support. Disseminated encephalomyelitis has been conceived of as an acute form of multiple sclerosis (18) and the striking resemblance between the acute lesions in the latter and the coalescent lesions in the former has been pointed out (17, 18). The occurrence of a postinfectious type of disseminated encephalomyelitis, and more particularly the development of a comparable pathological picture following the repeated injection of rabbit spinal cord in the Pasteur treatment for rabies, aroused the suspicion that immunological (allergic) factors might play a part in the production of demyelinating lesions (*cf.* reference 17).

Rivers, Sprunt, and Berry (1) and Rivers and Schwentker (2) provided the first experimental evidence that might support this theory and this was later confirmed by Ferraro and Jervis (3). By the prolonged intramuscular and subcutaneous inoculation of emulsions and extracts of rabbit brain into monkeys,

these investigators succeeded in producing multiple lesions in the central nervous system marked by their perivascular orientation, inflammation, and associated demyelination. Their distribution and appearance resembled somewhat those encountered in the human demyelinating diseases, more particularly disseminated encephalomyelitis. The great number of injections and the prolonged period necessary for the production of the lesions made this a somewhat cumbersome method for further study of the relationship between this experimental disease and its possible human counterparts. Since the use of adjuvants had so dramatically enhanced the production of antibodies to a variety of other antigens (4–13), and since it was suspected that the underlying phenomenon in this experimental disease might be due to an antigen-antibody reaction, the effect of adjuvants on the rapidity of production of the lesions was tested. By the technique described only a few injections, or even a single injection of either homologous monkey brain or of heterologous rabbit brain emulsion and short time intervals are required to elicit the syndrome, thereby permitting the use of many more animals, providing a greater material for study as well as a practicable method of assay to guide attempts at purification of the specific antigen involved. Similar experiments were carried out in white mice and guinea pigs in an attempt to find a more suitable animal but were negative.

The distribution of the lesions in our experimental animals bears a distinct resemblance to that in disseminated encephalomyelitis and multiple sclerosis of human beings. The white matter of the brain is chiefly affected with secondary or less striking involvement of the gray matter. There is some tendency to periventricular clustering of lesions and the pons, optic nerves, and the central white matter of the cerebellum bear the brunt of the pathological process, although it is constant and often severe in the white matter of the cerebrum as well. The perivascular position of the lesions, more particularly about venules and veins, is much like that in disseminated encephalomyelitis and has also been described sporadically in the other demyelinating diseases. The tendency to coalescence of the abnormal perivascular changes producing larger confluent lesions resembles a similar phenomenon seen in disseminated encephalomyelitis. It also gives rise to more extensive lesions which are comparable to those encountered in multiple and diffuse sclerosis. Occasional lesions at the outer borders of the brain stem, spinal cord, and optic nerves have the wedge-shaped contours of some encountered in multiple sclerosis. The degeneration of myelin which varies from slight perivascular pallor to massive destruction of myelin sheaths is, of course, the chief point of comparison. This coupled with a relative preservation of axones, further heightens the similarity. In some of the monkeys surviving for a longer time another feature of the pathological process was noted which seems to link it to multiple sclerosis as well as to disseminated encephalomyelitis. This is the presence of lesions of varying age set side by side or scattered in the central nervous system. These pathological resemblances of the

present experimental disease to multiple sclerosis and disseminated encephalomyelitis find their counterpart in some clinical parallels. The most prominent feature of the clinical picture in the monkeys is the variety of symptoms. Among these, ataxia, visual disturbances, and motor disabilities are prominent. The occurrence of remissions and relapses in some of the animals is striking.

Despite these points of similarity there are a number of important differences between the lesions produced experimentally and those of the human demyelinating diseases. The degree of inflammation observed in most of the monkeys is far beyond that usually encountered in the human diseases. This may depend in great part upon the fact that the monkeys usually were examined postmortem at a much more acute stage of the development of their lesions than is common in the human diseases referred to above. The massive infiltration by polymorphonuclear leucocytes, fibrin impregnation, and occurrence of hemorrhages described in the monkeys are rare in human demyelinating disease. (It is of interest that some of these acute and hemorrhagic lesions closely resemble those reported in the experimental production of the Arthus phenomenon in the brain of rabbits (19) and monkeys (20).) Acute hemorrhagic leucoencephalitis in the human being described by Hurst (21), later by Henson and Russell (22), and more recently by Wolf and Cowen (23), presented many of the features of this acute stage of the present experimental disease in monkeys. All of these investigators point out the close parallels between this leucoencephalitis and disseminated encephalomyelitis and believe that they may be linked etiologically. It may be that acute hemorrhagic leucoencephalitis represents an acute and violent form of disseminated encephalomyelitis equivalent to the acute stage of the present experimental disease in monkeys.

Another difference between the experimental and human conditions under discussion is the rather florid development of epithelioid-like mononuclear cells in and about the blood vessels of the brain in the monkeys. In our animals there was no associated giant cell formation although these were found regularly in the monkeys sensitized over a much longer period of time by the other investigators (1–3). This characteristic finds only rare and uncertain counterparts in the human pathology of demyelinating disease (17). The paucity of lesions in the spinal cord is also quite unlike that seen in most cases of disseminated encephalomyelitis or multiple sclerosis. It is true, however, that there may be considerable variation in the degree of this involvement in the human being. The degree of inflammation in the leptomeninges and the common occurrence of mild inflammatory changes in the choroid plexus and tela choroidea in the monkeys also served to differentiate the experimental process from the spontaneous human disease. Taken as a whole, however, these points of contrast do not appear to be crucial. They may possibly prove to be due to a species difference in response to a similar etiological mechanism,

to differences in the age of the pathological process as studied in the two species (the very early observation of lesions in the monkeys), and possibly to a better response in the anmals due to greater availability, dosage, or more effective route of administration of antigen.

The hypothesis that the experimental disease produced in monkeys by the injection of emulsions of rabbit or monkey brain involves the formation of antibodies to the injected brain tissue, which then react with antigen in the central nervous system of the animal to produce the disease, is supported by the following findings: The essential lesions in the monkeys are confined to the central nervous system. They appear to be specific for brain tissue since they cannot be produced by the injection of lung emulsions. Incorporation of adjuvants into the brain emulsion produces a dramatically enhanced response. The perivascular position of these abnormal changes is to be expected since circulating antibody would be required to pass through the vessel wall into the neural parenchyma to react with antigen and produce its first effects. The presence of small numbers of eosinophiles in the lesions, the lush development of epithelioid-like histiocytes, and the resemblance of some of the lesions to those produced in the Arthus phenomenon in the brain, also provide corroborative histological evidence for this concept. The failure to produce the lesions by injection of serum does not constitute an objection to this theory, since any antibodies formed as a result of the injections would be removed from the circulation by the tissues of the central nervous system of the actively immunized animals and their sera might not contain circulating antibody.

It does not seem probable that the abnormal changes in the blood vessel walls are the primary intermediate mechanism for the production of the perivascular lesions since no comparable vascular changes were found in other organs. Capillary and venous thrombosis were so infrequent as to render it extremely unlikely that vascular occlusion played anything but a secondary rôle. The thromboplastic properties of the brain tissue did not appear to be involved since negative results were obtained with lung tissue which is also highly thromboplastic. It seems much more likely that the antigen-antibody union in the perivascular tissue either directly or indirectly gave rise to the inflammatory reaction (and degeneration) both in the vessel wall and in the surrounding tissue. The mechanism by which the inflammatory reaction is brought about requires further study. Secondary effects due to circulatory impairment brought about by changes in local capillary permeability and clogging of the perivascular (Virchow-Robin) and tissue spaces by exudate might cause additional injury to the perivascular parenchyma. The greater effect upon myelin as compared to axones might be dependent either upon its generally greater susceptibility to any injury or perhaps to a specific effect of the antibody upon the myelin if the latter should prove to be the antigenic material.

In an attempt to identify the antigenic material more closely, fetal rabbit brain and separated cerebral gray and white matter of the monkey were employed with adjuvants. The attempt to secure pure gray or pure white matter could not of its nature be successful and as might be expected the monkeys inoculated with each showed the same effects as did those animals inoculated with whole monkey brain. The animals inoculated with fetal rabbit brain which was demonstrated to be free of myelin, however, never developed any lesions in or symptoms referable to the central nervous system, although they received more inoculations and were observed for a longer period of time than were the others. This may mean that myelin or some other substance present in the cerebrum of the adult rabbit (or monkey) and absent in the fetal animal may be the antigen involved. It may also indicate, however, that a substance other than myelin has not yet reached a stage of fetal development at which it becomes antigenic.

An added feature in the present experiments and in those of Morgan (15, 16) over those previously reported is the production of lesions by the use of homologous brain. Heretofore only heterologous brain, that of the rabbit, had been used. With the demonstration that similar effects can be produced with homologous tissue, autoimmunization as a possible mechanism in the production of comparable lesions in man must be considered. The manner in which the central nervous system of the individual may liberate tissue antigens stimulating antibody formation, which in turn react with the original tissue is difficult to surmise. It may be that in the postinfectious encephalomyelitides, pathological changes brought about by the infecting virus or other causative agent, result in the liberation of brain tissue in a form in which it is both antigenic and can reach the sites of antibody formation. It has been suggested that antibodies may be formed to homologous tissue proteins as a result of bacterial or viral infection (24) and indeed the findings that antibodies to normal lung tissue are produced in patients with primary atypical pneumonia (25) and that antibodies to human heart tissue were present in 75 per cent of patients with acute rheumatic fever (26) may be instances of such a mechanism. Many investigators consider positive Wassermann reactions to result from the liberation of the Wassermann antigen from the tissues as a consequence of syphilis or other diseases associated with positive reactions (27, 28). The demonstration by Kidd and Friedewald (29) that normal rabbit sera contained antibodies to a variety of tissue antigens also lends support to this concept.

The total lack of lesions in the peripheral nerves, retinae, or in neural tissue anywhere else in the body, other than in the central nervous system in the monkeys, paralleled that in the human demyelinating diseases. It is remarkable, however, that such tissues, presumably identical in substance with the brain and spinal cord (*e.g.* the white matter and peripheral nerves, the retina, and gray matter) except for their content of Schwann and connective tissue sheaths,

lack of glial cells (excepting the retina, etc.) should be entirely devoid of abnormal changes. Severe and extensive lesions in the optic nerves stopped abruptly at the optic papilla and did not involve the retina. The lack of involvement of the peripheral nerves may point to differing antigenic properties of this tissue.

The sole involvement of the optic system in one monkey and its almost exclusive implication in another were of interest. The optic nerves, chiasm, tracts, and lateral geniculate bodies were affected in whole or in part. It has long been suspected that some instances of optic neuritis in man may be fragments of multiple sclerosis or closely related to it. It may be that the distribution of lesions in these monkeys represents the experimental equivalent of such human cases.

SUMMARY

1. A picture resembling acute disseminated encephalomyelitis in the human being has been regularly and rapidly produced in *rhesus* monkeys by injection of emulsions of adult rabbit and monkey brain administered with adjuvants.

2. No lesions of the central nervous system resulted from injection of similar emulsions of fetal rabbit brain or adult rabbit lung.

3. A description of the gross and histological findings in the central nervous system is given and compared with features of human demyelinating disease.

4. The experimental findings are in accord with the hypothesis that antibody to the injected brain emulsion reacts with the tissues of the nervous system of the animal to produce the pathological changes.

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EXPLANATION OF PLATES

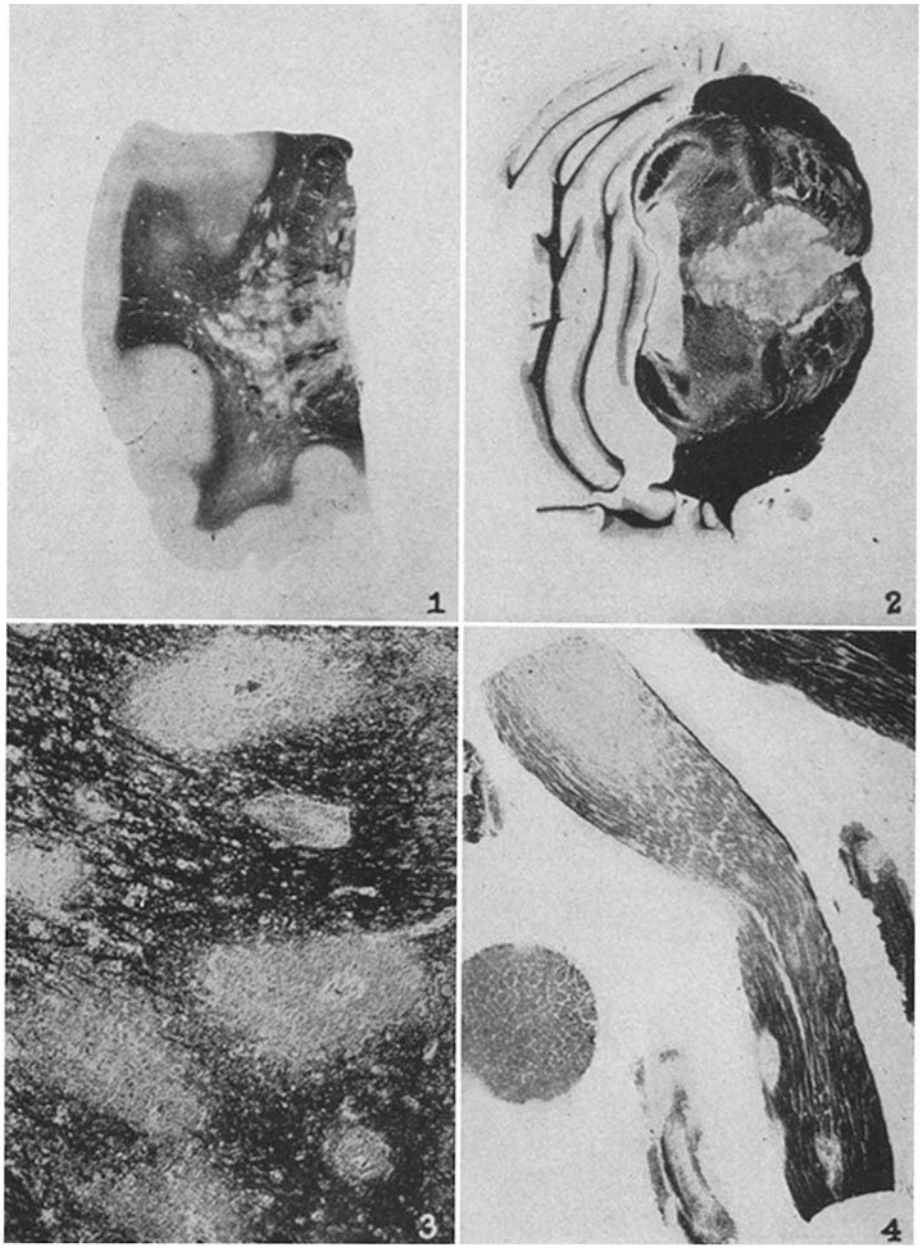
PLATE 1

FIG. 1. Multiple areas of perivascular demyelination in subcortical white matter of cerebrum. Lesions have frequently coalesced. Monkey 11. Mahon stain. ×3.

FIG. 2. Large coalescent area of demyelination in pons. Note marginal perivascular demyelination. Monkey 10. Mahon stain. ×3.

FIG. 3. Discrete perivascular zones of demyelination with early evidence of coalescence. Monkey 11. Mahon stain. ×60.

FIG. 4. Demyelinating lesions in optic nerve. Monkey 10. Mahon stain. ×9.



(Kabat *et al.:* Acute disseminated encephalomyelitis)

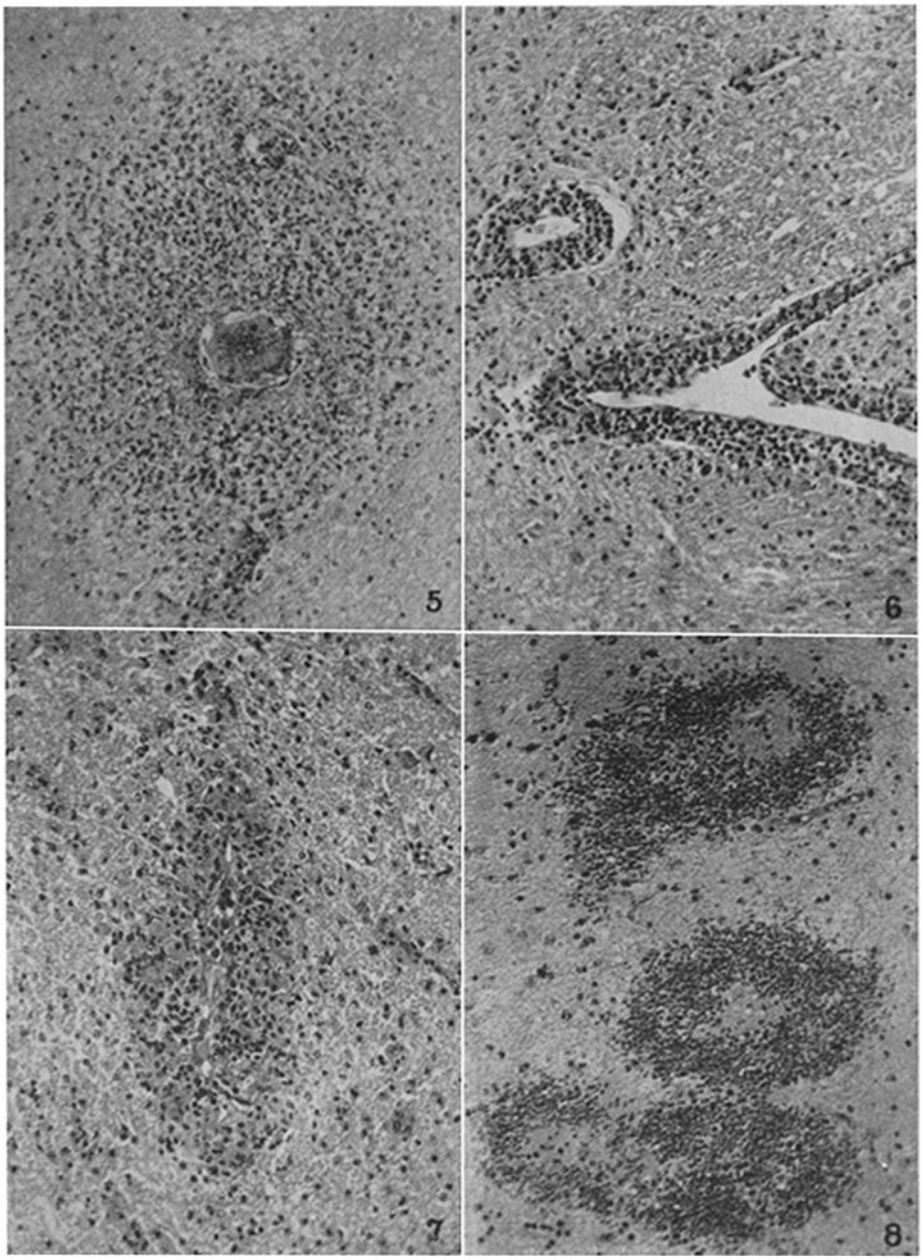
PLATE 2

FIG. 5. Mural and perivascular polymorphonuclear neutrophiles in acute lesion about venule. Monkey 9. Hematoxylin-eosin stain. ×90.

FIG. 6. Infiltration of wall and perivascular space of small vein by lymphocytes and occasional large mononuclear cells. Monkey 8. Hematoxylin-eosin stain. ×90.

FIG. 7. Pericapillary infiltration by large mononuclear, epithelioid-like elements in subcortical white matter. Monkey 8. Hematoxylin-eosin stain. ×90.

FIG. 8. Fresh, pericapillary hemorrhages at junction of cortex and white matter. Monkey 5. Hematoxylin-eosin stain. ×90.



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