ALLERGIC ENCEPHALOMYELITIS IN MONKEYS IN RESPONSE TO INJECTION OF NORMAL MONKEY NERVOUS TISSUE*

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Plates 3 and 4

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In an attempt to enhance the immune response of *rhesus* monkeys to poliomyelitis virus, Freund's adjuvant technique was employed. There resulted a striking but unexpected effect, already reported briefly (1, 2). The majority of monkeys showed signs of severe involvement of the central nervous system. These appeared 2 to 7 weeks after two or three subcutaneous injections of poliomyelitis-infected monkey spinal cord, incorporated into an emulsion containing a lanolin-like substance, paraffin oil, and heat-killed tubercle bacilli. Such signs as blindness, nystagmus, ataxia, spasticity, and general disorientation were observed, finally leading in most cases to complete prostration. The pathological change was as striking as the signs, ranging from large necrotic and hemorrhagic masses seen grossly to minute hemorrhages. Microscopic study of sections of the central nervous system revealed disseminated foci of intense perivascular and extravascular infiltration throughout the brain and to a lesser extent the spinal cord.

The effect of injection of poliomyelitis-infected monkey spinal cord incorporated into an emulsion with adjuvants could be reproduced by a similar emulsion of spinal cord or white matter of brain of normal monkeys, and to a lesser extent by cortical gray matter. No such reaction occurred when adjuvants were injected alone, or when infected spinal cord was given without the entire adjuvant complement including killed tubercle bacilli. Both peripheral nerve and kidney suspension with adjuvants failed to incite the reaction. This experience, which will be described, leads to the conclusion that the reaction observed was an organ-specific isoimmunization in response to injection of central nervous tissue with adjuvants. The results of similar findings in an independent investigation by Kabat, Wolf, and Bezer (3) are reported in an accompanying paper.

Freund's adjuvant technique, which consists of incorporation of antigen into an emulsion containing a lanolin-like substance, paraffin oil, and dry heat-killed tubercle bacilli, has resulted in greater antibody response to a variety of agents. By this method Freund and McDermott (4) induced in guinea pigs a sensitization to horse

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serum of long duration, characterized by high precipitin or colloidal agglutinin level. The presence of tubercle bacilli in the emulsion had a particularly striking effect on sensitization. Necrotic skin reactions to horse serum occurred frequently only in guinea pigs sensitized with horse serum emulsified in oil containing tubercle bacilli but not in those receiving horse serum with or without oil. Later Freund and Walter (5) showed that non-pathogenic acid-fast bacilli can be substituted for tubercle bacilli. Enhancement of antibody response in rabbits to diphtheria toxoid and to typhoid vaccine was demonstrated by Freund and Bonanto (6). To another bacterial antigen, *Shigella paradysenteriae* vaccine, Ehrich, Halbert, Mertens, and Mudd (7) showed not only prolonged antibody response but a reduction of the toxic effects by emulsification in falba and mineral oil.

That the adjuvant method improves immune response to virus antigens has been shown by Friedewald's (8) results with influenza virus. Not only was the antibody response in mice and rabbits greater and more prolonged to the virus mixed with mycobacteria, falba, and oil, than to virus in saline, but the immunity in mice to intranasal instillation of virus was far greater. Henle and Henle (9) demonstrated a far greater and more prolonged antibody response when human beings were vaccinated with a single subcutaneous dose of influenza viruses A and B when incorporated into an emulsion with falba and mineral oil than when given as a saline vaccine. The high level of antibody was present in serum taken 18 months after vaccination with antigen in the oily emulsion (10).

Although Kulka and Hirsch (11) report that allergy to pollen is demonstrable in animals only after an intensive course of sensitizing injections, they were able to induce sensitization and antibody response to ragweed extract in rabbits and guinea pigs far more vigorously by the adjuvant technique than by pollen extract alone Ragweed pollen extract plus adjuvants gave rise to serum antibody capable of passively transferring skin sensitization. Chase (12) found that antisera to horse serum and ragweed extract produced in guinea pigs by means of the adjuvant technique were more active in inducing passive transfer to subcutaneous or intracutaneous injection of the homologous antigen. Landsteiner and Chase (13) had earlier used this method for sensitizing guinea pigs with proteins conjugated with simple chemical compounds. The serum and peritoneal exudates induced passive transfer of sensitization.

Adjuvants were originally used in the present work for the purpose of enhancing antigenicity of poliomyelitis virus. Reference will be made later to the immune response. However, a superimposed phenomenon, manifested by a disseminated encephalomyelitis, accompanied by signs of severe involvement of the central nervous system, interfered with long term immunization.

This phenomenon, interpreted as an autoimmunization, is similar to what other investigators have observed after repeated injections of nervous tissue in experimental animals. Thus Rivers and Schwentker (14) by means of 46 to 85 intramuscular injections of aqueous emulsion alternating with alcoholic extract of normal rabbit brain produced pathological changes in seven of eight monkeys. Ferraro and Jervis (15) have given a detailed description of pathological changes induced by similar injections in monkeys, consisting of disseminated perivascular lesions with destruction of myelin

and accumulation of fatty granular cells. Both papers discuss the possible significance of this reaction in relation to encephalitis following rabies vaccination, postvaccinal encephalitis and that occasionally following such virus diseases as measles, and finally the possible light it might throw on multiple sclerosis and Schilder's disease.

The organ specificity of the antibody induced in response to injection of brain suspension has been well demonstrated.

Lewis (16) and Schwentker and Rivers (17) showed that the complement-fixing antibody was induced in rabbits in response to injections of aqueous suspension and alcoholic extract of rabbit brain. Although minor cross-reactions occur with other organs, the reaction is primarily organ-specific and shows no species specificity. Bailey and Gardner (18) in passive anaphylaxis experiments in guinea pigs established the organ specificity of the reaction. Guinea pigs passively sensitized with antiserum to vaccine made in brain broth reacted to extracts of brain, sciatic nerve, as well as a rat carcinoma, but not to extracts of a variety of other organs. Kopeloff and Kopeloff (19) have more recently shown production of antibrain antibodies in the monkey in response to repeated intramuscular injections of alcoholic extract of sheep brain incorporated into an emulsion with adjuvants. Many of the monkeys did not survive the extensive course of injections, but whether there were any signs of involvement of the CNS before death is not recorded. The sera fixed complement in the presence of alcoholic extracts of monkey, sheep, and rabbit brain, to a minor extent to testicle and kidney, but not to liver, lung, spleen, heart, and blood. Conversely, serum of monkeys immunized with alcoholic extract of sheep kidney and monkey red blood cell failed to react in the presence of brain extract.

Methods and Materials

Immature *M. rhesus* monkeys in good physical condition which gave a negative reaction to an injection of 0.1 cc. 1/10 dilution of old tuberculin in the upper eyelid were selected.

They were injected subcutaneously in the chest or abdominal wall in doses of 0.75 to 1 cc. of a mixture containing per cc.: 0.2 mg. heat-killed *M. tuberculosis*,[1] 0.5 cc. paraffin oil (Coleman and Bell), 0.25 cc. falba (Pfaltz and Bauer, Inc., New York—a lanolin-like adsorption base, said to be a mixture of beeswax, paraffin oils of varying viscosities, and oxycholesterine extracted from lanolin), and 0.25 cc. 20 per cent tissue suspension in saline. The tissue suspension and falba were mixed in a mortar and paraffin oil, into which the tubercle bacilli had been ground, was added, while mixing. The thick emulsion resulting could just be drawn up through a 20 gauge needle.

The following tissues were used: (1) Gray matter from the cerebral cortex from two normal monkeys was obtained by suction. It was impossible to avoid taking some white matter, which was estimated as about a 10 per cent contamination. (2) White matter from the same two normal monkeys was provided by the corpus callosum and internal capsule and was essentially free from gray matter. The gray or white matter was weighed and ground in a mortar; saline was added to make a 20 per cent suspension. (3) Spinal cord from two normal monkeys. Under ether anesthesia with sterile precautions the entire spinal cord was taken, after removing the meninges, including pia. By this method a creamy suspension of cord in sufficient saline to make a 20 per cent suspension could be obtained in a chilled Waring blendor

[1] I am grateful to Dr. Jules Freund for sending this preparation.

by running in a 4° refrigerator room for two periods of 3 minutes each, allowing time for cooling between the runs. (4) Poliomyelitis-infected cord. Cervial and lumbar segments of spinal cord were removed from monkeys sacrificed on the day estimated to be the height of paralysis resulting from intrathalamic injection of virus suspension. The two strains of poliomyelitis used were the Lansing strain isolated in 1939 by Dr. C. Armstrong from a fatal case in Lansing, Michigan, and the Riley strain obtained by Dr. David Bodian from the stool of a patient in Chicago during the summer of 1943. Pools of spinal cord of monkeys infected with one or the other strain were prepared in the same way as the normal spinal cord, as described above. (5) Kidneys from the same two normal monkeys which provided the normal spinal cord were similarly ground in the Waring blendor. (6) Peripheral nerves were ground with great difficulty with a mortar and pestle using alundum as an abrasive. Four monkeys (B3-79 through B3-82) were given a suspension of sciatic nerve from a single normal monkey, sacrificed under anesthesia; five other animals (B8-49 through B8-53) received a pool of peripheral nerves from four individuals, consisting of sciatic, median, and radial nerves.

The results of inoculation of tissue suspension with adjuvants are shown in Table I. In most cases the onset of signs was from $2\frac{1}{2}$ to 5 weeks after injection, the earliest was 14 days and latest 7 weeks. Animals showing no reaction were observed for 6 to 7 weeks before sacrifice. Positive reactors occurred only in the groups given normal monkey gray matter (2 out of 9), white matter (8 out of 10), spinal cord (8 out of 12), or poliomyelitis-infected spinal cord (8 of 9) emulsified with the adjuvants: falba, paraffin oil, and heat-killed tubercle bacilli. In a group of five animals which received injections of poliomyelitic spinal cord in paraffin oil and falba, but no tubercle bacilli, no positive reactions were observed. Nor was there any reaction to peripheral nerve (9 individuals), kidney suspension (4), or saline (8) when each was mixed with the full complement of adjuvants.

The low proportion of reactors which appeared in response to adjuvant-emulsion of normal monkey gray matter suggests that this might be due to unavoidable contamination with white matter to which only an unusually sensitizable individual would react. Aside from the technical difficulty of obtaining "pure" gray matter, any area of gray contains a certain number of myelinated nerve fibers. The "incubation period" in the group given adjuvant-emulsion of white matter is strikingly shorter than that in the group injected with spinal cord. Either white matter of brain is more effective than that of cord or, more likely, there is a greater concentration of antigen in selected white matter, the white matter of cord being diluted to the extent that it includes gray matter. It is interesting that only in the group of monkeys injected with cerebral white matter emulsion were there individuals who had CNS lesions without having shown obvious signs. Five out of ten showed signs but an additional three monkeys whose appearance was not more than questionable had typical pathological changes in the CNS ranging from mild to severe degree of involvement.

Of the many monkeys in various laboratories which have been vaccinated subcutaneously with poliomyelitis-infected monkey cord without adjuvants,

occasional ones develop poliomyelitis, but none has been reported to show the disseminated encephalomyelitis described here.

Recent experience in this laboratory includes eleven monkeys vaccinated subcutaneously with four to twelve doses of 5 to 20 per cent suspension of Lansing virus, under observation for 4 to 7 months, without showing signs. Nor did any signs appear in another group of fifteen monkeys observed 5 months which received six subcutaneous doses of 5 per cent suspension of Riley virus inactivated by formalin or ultraviolet light, or in four monkeys given a similar course of injections of active virus, Riley strain (one of these showed quadriplegia typical of poliomyelitis, but improved and lived to the end of the 5 months' observation period).

Thus none of thirty monkeys observed several months after subcutaneous injection of active virus in monkey spinal cord has shown signs of disseminated encephalomyelitis. This is in contrast to the sixteen positive reactors of twenty-one animals injected with spinal cord (whether infected or not) incorporated into an emulsion with adjuvants, and indicates the enhancement of antigenicity by this technique.

Pathology.—Among the positive reactors a variety of signs was shown reflecting the widespread distribution of lesions in the brain and spinal cord. Blindness was the most striking sign; spasticity, ataxia, and nystagmus were frequently observed, as well as disorientation and occasional paralysis. Eosinophilia was not found. The spinal fluid was often turbid at time of sacrifice. Fever was irregularly present. In many instances the general condition of the animals deteriorated rapidly and they were sacrificed a few days after the onset of signs, although some of them might have survived.

Gross examination of the brain frequently revealed areas of abundant petechial hemorrhages and occasionally large brown masses of hemorrhage and softening, such as that shown in the left frontal lobe and right caudate nucleus in B6-64 (Fig. 1). This animal was found dead the day after appearance of ataxia, spasticity, and general dazed condition, which developed $3\frac{1}{2}$ weeks after injection; his right arm was weak and his eyes deflected to the right.

Microscopically, foci of intense perivascular and extravascular infiltration were seen disseminated irregularly throughout the brain and to a lesser extent the spinal cord. The cellular reaction consisted of a mixture of cells of the mononuclear series and polymorphonuclear leukocytes among which eosinophils were present and sometimes predominated. No giant cells were seen. In the regions of more severe reaction, there was focal necrosis and hemorrhage. Demyelination was present on the periphery of these areas of intense reaction. The encephalopathy is similar to that observed by Rivers and Schwentker (14) and by Ferraro and Jervis (15). The more chronic nature of the reaction in their animals may account for the greater degree of demyelination and giant cell formation. Figs. 2 to 4 show sections of the brain of B1-77 who seemed to be going blind 4 weeks after injection of emulsion of poliomyelitis-infected cord

TABLE I

Allergic Encephalomyelitis in Monkeys in Response to Injection of Various Materials with Adjuvants

Subcutaneous injection	Amount and No. of injections	Monkey No.	Time of onset of signs	Cardinal signs	Lesions: CNS	Lesions: Other	+ reactors / No. injected
Normal monkey cortical gray matter + falba + paraffin oil + heated tubercle bacilli	1 cc. 3 times	C7-2		None. Sacrificed 7 wks.	0		
		C7-3		None. Sacrificed 7 wks.	0		
		C7-4		None. Sacrificed 7 wks.	0		
		C7-5		None. Sacrificed 7 wks.	0		
		C7-6	5 wks.	Weak left leg and arm.			2/9
		C7-7		None. Sacrificed 7 wks.	0		
		C7-8		None. Sacrificed 7 wks.	0		
		C7-9	17 days	Ataxic, weak			
		C8-0		None. Sacrificed 7 wks.	0		
		C8-1		None. Died at 3.5 wks.			
Normal monkey cerebral white matter + falba + paraffin oil + heated tubercle bacilli	1 cc. 3 times	C8-2		None. Sacrificed 7 wks.	+		
		C8-3	17 days	Dazed, disoriented			
		C8-4	15 days	Ataxic, blind			
		C8-5	14 days	Nystagmus, ataxia			
		C8-6		None. Sacrificed 7 wks.	+		8/10
		C8-7	3 wks.	Blind, pupils dilated			
		C8-8		None. Sacrificed 7 wks.	0		
		C8-9		None. Sacrificed 7 wks.	+		
		C9-0		None. Sacrificed 7 wks.	0		
		C9-1	17 days	Nystagmus. Paralysis	+		
Normal monkey cord + falba + paraffin oil + heated tubercle bacilli	1 cc. 2 times	B2-73	4 wks.	Blind	+	0*	
		B2-74		None. Tuberculosis. Sacrificed 6 wks.	0	Tubercles	
		B2-75	5 wks.	Dazed, tremulous	+	0	
	1.5 cc. 2 times	B3-75		None. Sacrificed 7 wks.‡	0		
		B3-76	6 wks.	Blind	+	0	
		B3-77		None. Sacrificed 7 wks.‡	0		8/12
		B3-78		None. Sacrificed 7 wks.‡	0		
	1 cc. 3 times	B6-61	4 wks.	Rigid and weak, falls	+		
		B6-62	6 wks.	Paralyzed, disoriented, blind	+		
		B6-63	16 days	Incoordinated, thrashing	+		
		B6-64	3.5 wks.	Dazed, ataxic, spastic	+		
		B6-65	5 wks.	Ataxic. Nystagmus	+		
Poliomyelitis infected monkey cord + falba + paraffin oil + heated tubercle bacilli	1 cc. 3 times (Lansing)	B1-71	3.5 wks.	Spastic, paretic. Nystagmus	+	0	
		B1-72	3.5 wks.	Blind. General deterioration	+		
		B1-73	5 wks.	Blind	+	0	
		B1-74		None. Kept 10 mos.			8/9
		B1-75	3 wks.	Blind. Died	+	0	
	1 cc. 3 times (Riley)	B1-77§	4 wks.	Blind. Clonic seizures	+		
		B1-78	5 wks.	Found dead	+	0	
		B1-79	4 wks.	Legs, arms, eyelids paralyzed	+	0	
		B1-80	7 wks.	Blind	+	0	
Poliomyelitis infected monkey cord + falba + paraffin oil	1 cc. 2 times (Lansing)	B2-79‖		None. Sacrificed 5 mos.	0		
		B2-80		None. Sacrificed 3 mos.	0		0/5
		B2-81‖		None. Observed 4 mos.			
		B2-82‖		None. Observed 4 mos.			
		B2-83		None. Emaciated; died 2 mos.			

TABLE I—*Concluded*

Subcutaneous injection	Amount and No. of injections	Monkey No.	Time of onset of signs	Cardinal signs	Lesions		+ reactors / No. injected
					CNS	Other	
Peripheral nerve + falba + paraffin oil + heated bacilli tubercle	1.5 cc. 2 times divided	B3-79		None. Sacrificed 7 wks.	0		
		B3-80		None. Sacrificed 7 wks.	0		
		B3-81		None. Sacrificed 7 wks.	0		
		B3-82		None. Sacrificed 7 wks.	0		0/9
	1 cc. 3 times	B8-49		None. Sacrificed 7 wks.	0	0*	
		B8-50		None. Sacrificed 7 wks.	0	0*	
		B8-51		None. Sacrificed 7 wks.	0	0*	
		B8-52		None. Sacrificed 7 wks.	0	0*	
		B8-53		None. Sacrificed 7 wks.	0	0*	
Kidney + falba + paraffin oil + heated tubercle bacilli	1.5 cc. 2 times divided	B3-83		None. Sacrificed 7 wks.‡	0	0	
		B3-84		None. Sacrificed 7 wks. Tuberculosis	0	Tubercles	0/4
		B3-85		None. Sacrificed 7 wks.‡	0	Tubercles	
		B3-86		None. Sacrificed 7 wks.	0	0	
Saline + falba + paraffin oil + heated tubercle bacilli	1 cc. 2 times	B2-76		None. Sacrificed 6 wks.	0	0	
		B2-77		None. Sacrificed 6 wks.	0	0	
		B2-78		None. Sacrificed 6 wks.	0	0	0/8
		B6-66		None. Sacrificed 6 wks.	0		
		B6-67		None. Sacrificed 6 wks.	0		
		B6-68		None. Sacrificed 6 wks.	0		
		B6-69		None. Sacrificed 6 wks.	0		
		B6-70		None. Sacrificed 6 wks.	0		
Poliomyelitis infected monkey cord¶	4–12 times						0/30

* Sciatic nerves normal microscopically.

‡ Red hepatization of lung.

§ A fifth animal, B1-76, in this series showed quadriplegia on the 9th day. Distribution and type of lesions in CNS typical of poliomyelitis.

‖ Given an additional subcutaneous injection at 3 months.

¶ For details, see text.

in adjuvants. Four days after first appearance of blindness he was found crouching in the corner of his cage, quivering. Two days later he was prostrate and tense, his pupils dilated. He frequently went into clonic seizures; he was sacrificed at this time. The lesions in the lateral geniculate body would readily account for the blindness. Fig. 4 emphasizes the perivascular nature of the lesion. The widespread distribution of lesions in Figs. 2 and 3 is typical, although more severe than in many cases, of this encephalopathy. Its apparently random distribution around the small vessels throughout the brain and the prominence of lesions in the white matter of the cerebrum clearly differentiate it from poliomyelitic lesions. Fig. 5 is a section at the level of the optic chiasm of B1-72 where the intense lesions give sufficient explanation for the blindness observed at $3\frac{1}{2}$ weeks. There is also conspicuous involvement of

the red nucleus bilaterally. Fig. 6 shows the spinal cord of B1-79 at the level L7. Four weeks after injection of poliomyelitis-infected cord with adjuvants this animal presented ptosis of the eyelid and paralysis of arms and legs. Intense perivascular reaction occurred in gray and white matter alike. This distribution of the infiltration and lack of motor neuron destruction is very different from the picture characteristic of poliomyelitis. In animals in which the spinal cord was involved, often the posterior roots only, but sometimes the meninges as well, were affected. The reaction in the cord was regularly less intense than in the brain.

Organs examined other than the CNS included lung, liver, spleen, and kidney (and, where noted, sciatic nerve). Twelve to fourteen of each of these organs were examined and no perivascular reaction was noted. Other incidental pathological findings are recorded in Table I.

Passive Transfer.—Two attempts to transmit the encephalitic effect to normal monkeys by means of serum of affected monkeys in the acute phase have failed.

(1) Normal *rhesus* B3-72 was given intraperitoneally 20 cc. serum of B2-73 taken the day of onset of blindness which set in 4 weeks after two subcutaneous injections of an emulsion of normal monkey cord, falba, paraffin oil, and tubercle bacilli. The monkey receiving the serum showed no signs nor was there any change in the central nervous system either grossly or microscopically, when it was sacrificed 6 weeks later. (2) Serum was taken from B1-80 when he was going blind 7 weeks after two subcutaneous injections of Riley virus-infected monkey cord emulsified with falba, oil, and tubercle bacilli. 20 cc. of this were given intraperitoneally to another normal monkey B3-73 and 9 days later 13 cc. more by the same route. He was sacrificed at 6 weeks; no gross or microscopic lesions were seen in the brain. Further attempts at passive transfer will be undertaken.

Antibody Response to Lansing Poliomyelitis Virus.—Since most of the animals were sacrificed between $3\frac{1}{2}$ and 5 weeks after injection of Lansing poliomyelitis virus emulsified with adjuvants it was not possible to follow the course of serum antibody production.

However, the serum of four of eight monkeys alive at 1 month neutralized Lansing virus with a titer of about 1/10, in intracerebral mouse neutralization tests. Of a group of five which received Lansing virus in falba and paraffin oil (without tubercle bacilli) only one showed neutralizing antibody, with a titer of 1/4. In a total of eleven monkeys given subcutaneous injections of various doses of Lansing virus without adjuvants, three showed antibody at 1 month, ranging in titer from 1/2 to 1/30. One monkey, B1-74, who received three injections of Lansing virus with adjuvants and failed to develop allergic reaction was observed for 7 months. The serum antibody level from 1 to 7 months fluctuated in titer between 1/2 and 1/200, which is considered only a moderate antibody level.

No conclusion can be drawn as to whether there was a greater degree of antibody response at one month attributable to the use of adjuvants, and the response over longer periods could not be established.

DISCUSSION

The disseminated encephalomyelitis induced in monkeys corresponds to that described by Rivers and Schwentker (14) and later, with a more detailed description of the encephalopathy, by Ferraro and Jervis (15). In the earlier reports the effect was induced by a great number of injectons of CNS antigen. In the present study, as in the accompanying report by Kabat, Wolf, and Bezer (3), by incorporation of antigen into an emulsion with adjuvants according to Freund's technique this encephalopathy was readily induced. Thus a means for studying the reaction is available.

Emulsions of adjuvants with white matter of normal monkey brain or spinal cord (whether normal or poliomyelitis-infected) show the highest rate of positive reactors; a lower rate was induced by emulsion of cortical gray matter; and none by peripheral nerves. The occasional positive reactor to gray matter may be accounted for by contamination with white matter which could not be avoided. Thus the antigen is present in white matter, tentatively not in gray matter, and not in peripheral nerve. Glia could hardly be responsible since they would be as fully represented in gray matter. Axoplasm and myelin would be common to white matter and peripheral nerve. Perhaps the essential difference lies in the nature of the myelin of the cerebral white matter as contrasted to that of peripheral nerve. By further experiments we are attempting to define what component of the central nervous system is responsible for the reaction.

The bearing of the mechanism of this phenomenon on multiple sclerosis, "diffuse sclerosis," and demyelinating encephalomyelitides is a subject for interesting speculation. Ferraro (20) and Putnam (21) give thorough reviews of these various conditions which leave little doubt about the similarity of the encephalopathies when one takes into account intensity and chronicity of the individual cases. The closest parallel with the induced reaction is the occasional occurrence of encephalitis following rabies treatment which consists of multiple injections of inactivated virus in CNS tissue. It is hardly necessary to warn against the promiscuous use of adjuvants until the nature of all the antigenic effects which may be enhanced are appreciated. This study, for example, was initiated to enhance antibody response to poliomyelitis virus but sensitization to the CNS menstruum overwhelmed the anticipated result.

SUMMARY

By subcutaneous injection of central nervous tissue emulsified with adjuvants according to Freund's technique it has been possible to induce in the majority of monkeys an acute disseminated encephalomyelitis which is interpreted as an isoimmunization to CNS tissue. Positive reactions occurred only in response to CNS tissue containing white matter; *i.e.*, cerebral white matter, spinal cord (whether normal or poliomyelitis-infected), and cortical "gray" matter (with an

estimated 10 per cent contamination with white matter). No reaction occurred when peripheral nerve or kidney suspension or saline alone was injected with adjuvants. The perivascular and extravascular infiltration induced was confined to the CNS.

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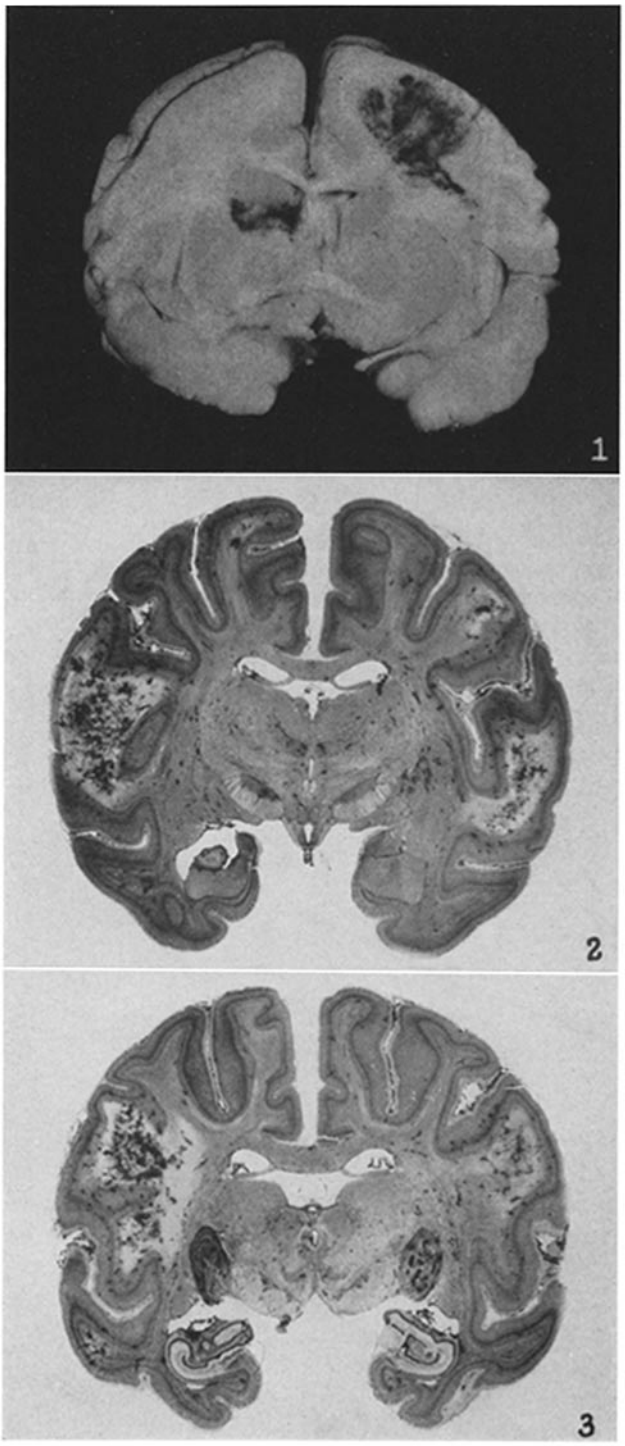
EXPLANATION OF PLATES

PLATE 3

FIG. 1. Transverse section of brain of B6-64. Massive regions of hemorrhage and softening in left frontal lobe and right caudate nucleus. × 1.3.

FIG. 2. Gallocyanin. Transverse section of brain of B1-77 at level of thalamus. Disseminated foci of intense perivascular and extravascular infiltration prominent particularly in white matter of the cerebrum, but present throughout the section. × 1.4.

FIG. 3. Gallocyanin. Transverse section of brain of B1-77 through midbrain at level of NIII. Marked infiltration in white matter of cerebrum and also in lateral geniculate bodies as well as generally disseminated. × 1.4.



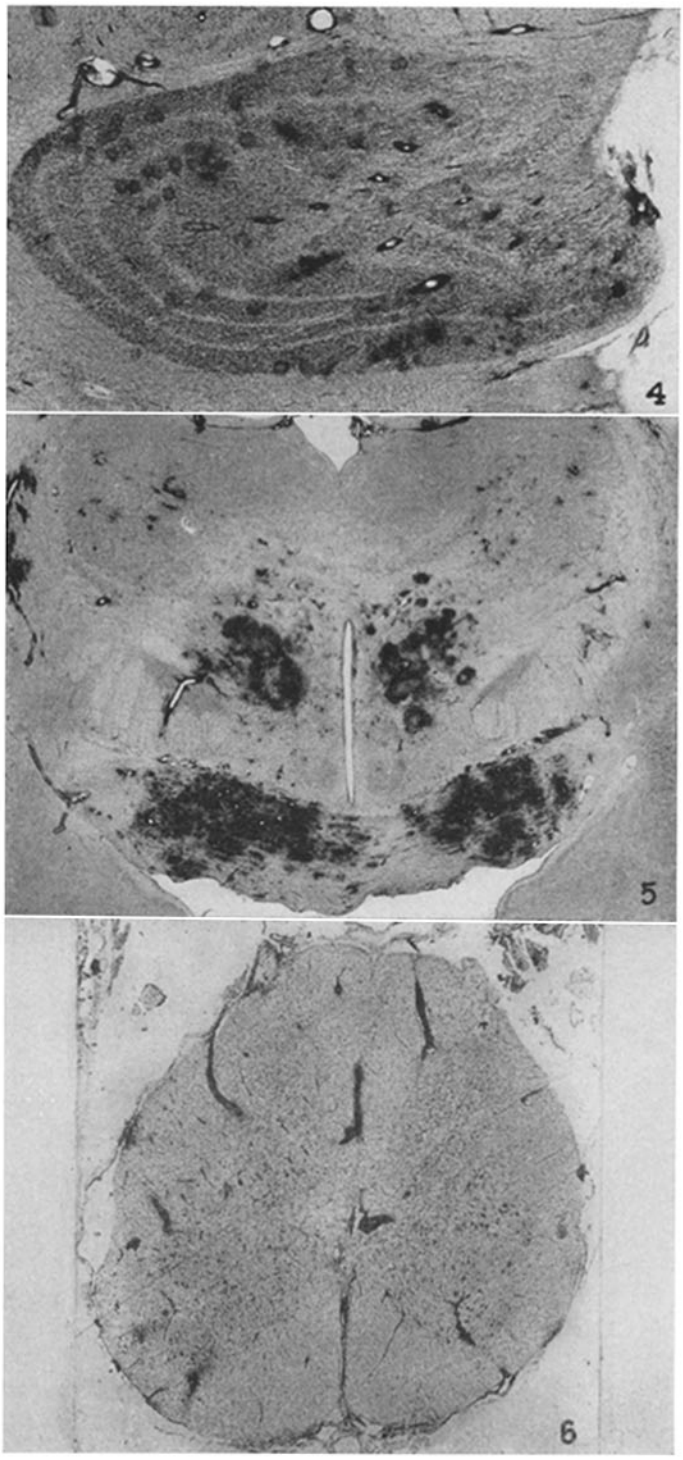
(Morgan: Allergic encephalomyelitis in monkeys)

PLATE 4

FIG. 4. Gallocyanin. Higher magnification of right lateral geniculate body of B1-77. The perivascular distribution of the intense infiltration is apparent. × 12.

FIG. 5. Gallocyanin. Transverse section of brain of B1-72 at level of optic chiasm. Massive perivascular infiltration, particularly in optic chiasm and red nuclei. × 4.

FIG. 6. Gallocyanin. B1-79 transverse section of spinal cord at L7. Perivascular infiltration in gray and white matter. × 11.



(Morgan: Allergic encephalomyelitis in monkeys)