NON-PARALYTIC POLIOMYELITIS IN THE CHIMPANZEE*

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Plates 15 to 19

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Soon after the obvious manifestations of poliomyelitis had been clearly described, it was evident to such discerning investigators as Caverly (1, 2) and Wickman (3) that the full blown epidemic and the paralytic case are only high lights in a larger and more obscure epidemiological picture. In recent years, more attention has turned toward the obscurities of the non-paralytic and inapparent infections which these early observers recognized, since it seems clear that much of practical epidemiological and immunological moment will depend on elucidation of their natural history in interepidemic as well as in epidemic periods. Efforts to study inapparent infections, or even the mild non-paralytic ones, cannot of course be adequate until experimental tools now available are fully employed. Among these may be mentioned the detection of virus in contents of the alimentary tract (stools and pharyngeal secretions) by monkey inoculation, and the determination of increase in neutralizing antibody titer of serum after a presumed infection. In the experimental animal, in addition to these methods, one has recourse also to a histopathological analysis of infected nervous tissues at any stage of the disease, a procedure which although laborious, has already been shown to be of considerable value. We have previously summarized evidence showing that greatly varying degrees of pathological reaction may occur in the central nervous system as result of non-paralytic poliomyelitis in *rhesus* monkeys (4–6). Histopathological findings in non-paralytic poliomyelitis in monkeys had also been described by Sabin and Ward (7), and earlier by Kling *et al.* (8, case B. E. N. 10), although we are unable to accept Kling's diagnostic criteria in monkeys showing only meningeal lesions (9; see also Bodian and Howe, 5). Our previously published reports presented evidence from 2 chimpanzees as well as *rhesus* monkeys, but it is now possible to amplify this evidence with detailed information from additional chimpanzees in which non-paralytic poliomyelitis has been established. The chimpanzee, although a cumbersome experimental animal, is the animal of choice for such experiments since it is perhaps the only animal which sufficiently resembles man with respect to poliomyelitis to be of any considerable value for direct analogy, as well as for suggesting leads for study of the human disease in its inapparent form. It not only exhibits a clinical and pathological

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picture resembling that in man but has also been shown to eliminate virus in its stools (6), and to be susceptible to spontaneous infection in the inapparent form (10), as well as in the paralytic form (11).

Material and Methods

The material available for this study consists of 13 chimpanzees which have given evidence of having had non-paralytic poliomyelitis. Eight of these animals have been subjected to a detailed histopathological analysis of nervous tissues in the acute stage, and the others in later stages. In addition, 4 acute paralytic and 1 convalescent paralytic chimpanzee, and 4 non-infected animals were available for control comparison of the microscopic appearance of the nervous tissues. Animals were killed by the routine method of exsanguination under chloroform-ether anesthesia. With precautions for asepsis, tissues and stool were removed in most cases for virus isolation, and the carcass then embalmed with 3 liters of 10 per cent formol containing 1 per cent glacial acetic acid. The fixing fluid was preceded by about 200 cc. of normal saline to wash out blood. The central nervous system and peripheral spinal and autonomic ganglia were regularly removed for histopathological studies. The brain was embedded in celloidin and sectioned at 30 and 60μ, and blocks of spinal cord and all peripheral ganglia were embedded in paraffin and sectioned at 15μ. Every 20th section of the brain stem, and selected regions of the cerebral cortex were stained with gallocyanin and examined to determine the nature, severity, and distribution of lesions as compared with those shown to be characteristic of the paralytic disease in monkeys, chimpanzees, and man (6, 12). In addition complete serial sections of the olfactory bulbs, several blocks of spinal cord, and of various peripheral ganglia[1] were stained with gallocyanin and examined. Serum was obtained immediately preceding and at various times after inoculation. Stools obtained before and after inoculation were instilled intranasally in *rhesus* monkeys according to the method previously described (13). Such intranasal inoculations of simply prepared, untreated stool suspension over a period of 7 days gave a remarkably high proportion of "takes" (14). The material used for inoculation of the chimpanzee is recorded in the protocols and for the most part consisted of human stool suspensions obtained from three different epidemic sources. All materials inoculated in the chimpanzee were shown to produce poliomyelitis when previously inoculated into *rhesus* monkeys. Daily rectal temperatures were obtained in all animals following inoculation.

PROTOCOLS

Our findings have been summarized in Table I. Detailed protocols of the acutely paralytic controls (A83, A71, A1-05, A1-06), listed in Table I, have been published elsewhere in another connection (6), and will not be repeated here. As shown in Table I, the distribution of lesions in their nervous tissues is representative of animals inoculated by the nasal, gastric, and oral routes respectively. The brain centers listed in the table are those most commonly involved in fully developed paralytic cases (12), and it will be noted that in one paralytic case (A48, facial paralysis) the full distribution of lesions usually seen was not attained during the course of the disease. This is of some interest because, as will be shown, there is considerable likelihood that this paralytic infection was preceded by an unrecognized non-paralytic attack.

[1] The details concerning pathological findings in the peripheral ganglia will be published separately.

TABLE I

Distribution of Lesions in Nervous Tissues of Chimpanzees

	Paralytic cases, Portal of inoculation						Non-paralytic cases, Portal of inoculation							Chronic cases, Portal of inoculation							Normal chimpanzees			
	Nasal	Gastric			Oral		Nasal	Oral	Oral-gastric					Oral			Nasal	Oral	Par. cereb.	Nasal				
	A83	A71	A1-05	‡A48[1]	A48[2]	A1-06	A1-75	A3-92	A4-34	A4-35	A4-36	A4-47	A4-48	A5-01	‡A3-91	‡A3-58	‡A5-27[a]	A5-27[b]	A5-27[c]	A1-74[1]	‡A1-74[2]	A1-01	A1-00	A1-73	A8-07
Brain																								
Olfactory bulbs	cccc****	—	—		—	—	cc***	cc**	—	—	cc**	—	c	cc*	c*	—			—		cc*	—	—	—	
Secondary olf. centers	cccc****	—	—		—	—	c***	—	—	—	c	—	c	c	c	—			—			—	—	—	—
Preoptic area and hypothal.	ccc***	c*	cc**		—	c*	*	cc*	c*	—	c	c	c	—	c	—			—	c*		—	—	—	—
Globus pallidus	cccc****	cc*	—		—	c	—	c	—	—	c	c	—	—	—	c			—	c*		—	—	—	—
Motor cortex	cc**	cc**	c		—	c*	—	c*	c**	—	c	c*	c*	c	*	c			—	c*		—	—	—	—
Lateral thalamus	ccc***	cc**	—		—	c**	—	cc	c*	c*	c	—	cc*	—	c	—			—	c*		—	—	—	—
Subthalamus and midbrain	ccc***	cc**	cc*		—	ccc**	—	c*	cc**	—	c	c	c*	c	c	c			—	cc*		—	—	—	—
III nuclei	cccc****	—	—		—	cccc***	—	—	—	—	—	—	—	—	—	—			—	c		—	—	—	—
Cerebellar cortex	ccc**	—	—		—	—	—	—	*	ccc**	—	—	—	—	—	—			—	—		—	—	—	—
Nuclei fastigii	cccc****	c*	c*		—	cc****	—	c**	c	—	c	c	c	—	—	—			—	—		—	—	—	—
Reticular formation	cccc****	ccc***	ccc***		—	ccc****	—	cc**	cc**	c	c	c	c*	—	—	c			—	c*		—	—	—	—
V nucleus (motor)	cc****	ccc***	cc*		—	c****	—	c	—	c	c	—	—	—	—	—			—	c		—	—	—	—
V nucleus (sensory)	cc***	ccc***	c*		cc*	c*	—	c	c*	c	—	—	—	—	—	c			—	—		—	—	—	—
VII nucleus (motor)	cc****	c	c*		cc**	ccc****	—	c*	c	c	—	—	—	—	—	—			—	—		—	—	—	—
Vestibular nuclei	cccc****	ccc****	cc***		—	cc****	—	c***	c***	—	—	c	—	—	—	—			—	c*		—	—	—	—
IX, X nuclei (sensory)	cccc***	c	cc		c	c*	—	—	—	—	—	—	—	—	—	—			—	—		—	—	—	—
X nucleus (motor)	c*	c	c*			cc***	—	—	—	—	—	*	—	—	c	—			—	—		—	—	—	—
XII nucleus	cc**	c	c**		c	c*	—	—	c	—	—	—	—	—	—	—			—	—		—	—	—	—
Spinal cord																								
Cervical	cc****	cc**	cc***	**	c	ccc***	—	c**	cc***	—	—	—	—	—	c	—			—	c**		—	—	—	—
Lumbar	cc**	cc***			—	cc**	—	cc**	c***	—	—	—	—	—	c	c			—	c**		—	—	—	—
Days after inoculation																								
Virus in stools	+6	−9	+5		−27, 33	+5	−7, 17	+12, 28	+6, 19	+6, 22	+21	+19, 28	+19	+19	+21, 53	−13, 29	+3–38	−4–23	−2–17	−0, 10	−11				
Autopsy	6	9	5	260	33	5	17	28	19	26	21	28	28	27	136	223	196	88	50	76	13				

c, perivascular cuffing. * Neuronophagia or mesodermal-glial infiltration. [1, 2] 1st and 2nd attacks. [a, b, c] 1st, 2nd, and 3rd inoculations. ‡ Non-paralytic attack. Total extent of lesions unknown in A48[1].

History and Findings in Non-Paralytic Instances

Experiment A1-75.—

Oct. 18, 29, 30, and 31, 1940. This chimpanzee, an adult tuberculous male, with severe cage paralysis of all extremities, was inoculated intranasally with a pool of human stool suspensions of known virulence (Baltimore, 1939), 1 cc. being instilled into each nostril. During the following days his temperature was irregular, and he apparently had a tuberculous pneumonia. Stool obtained on Oct. 27 failed to produce poliomyelitis in a *rhesus* monkey inoculated intranasally.

Nov. 5. Animal died, without having shown any signs of poliomyelitis. The lungs showed far advanced tuberculosis, with bilateral tuberculous pneumonia and fibrous pleuritis. There was extensive caseous tuberculosis involving all of the thoracoabdominal lymph nodes and most of the abdominal viscera. Stool obtained on this day was inoculated intranasally into a *rhesus* monkey, which subsequently failed to show evidence of poliomyelitic infection.

Summary of Microscopic Findings.—Histological sections revealed numerous lesions characteristic of poliomyelitis in the olfactory bulbs and secondary olfactory centers, and in no other parts of the nervous system examined (6). Spinal cord sections showed some nerve cell atrophy and loss, characteristic of cage paralysis, but no lesions of poliomyelitis. There were no tuberculous lesions in the central nervous system.

This case is of considerable interest because it represents the arrest of the pathological process of poliomyelitis in an extremely early stage, and localized to the region of the brain at and near the site of ingress, in an animal which received an inoculation that in a healthy animal (A83, Table I) was sufficient to produce a severe attack of poliomyelitis. One cannot help speculating whether the arrest in this case was due to the preexisting disease, either the tuberculosis or malnutrition, or both.

Experiment A3-92.—

Dec. 7, 1942. Chimpanzee "Rosebud" was a 3 year old female in excellent physical condition. She was bled for serum at the dealer's office where she remained until Jan. 5, 1943.

Jan. 6, 1943. Given 18 cc. of human stool suspension (Sudeck) by mouth. The suspension was taken with some resistance but after being mulled around in the mouth for several minutes, was swallowed completely. While the animal was held down a small amount of stool escaped from the mouth and ran into the left nostril. Two *rhesus* monkeys inoculated with this material subsequently became paralyzed on Jan. 24.

Jan. 7. Received 13 cc. of Sudeck stool by mouth, without anesthesia.

Jan. 20. Stool obtained on this day produced paralytic poliomyelitis in 2 *rhesus* monkeys inoculated intranasally.

Feb. 7. Animal has shown no signs of clinical poliomyelitis, and daily rectal temperatures, since the day of inoculation, have been within normal levels. She was nevertheless anesthetized and sacrificed. Stool obtained on this day produced paralytic poliomyelitis in 2 *rhesus* monkeys inoculated intranasally.

Summary of Microscopic Findings.—Although this animal had at no time shown any signs suspicious of poliomyelitis, the brain and spinal cord contained abundant lesions entirely characteristic of poliomyelitis, and of moderate severity (Figs. 1–3). The spinal cord lesions included a large number of cells showing neuronophagia (Fig. 3), but the distribution of destroyed motoneurons was so scattered that paralysis did not result. The distribution of lesions in the brain was characteristic of that seen after intranasal inoculation since the olfactory bulbs were definitely involved (Fig. 1). It therefore appears that accidental contamination of the nasal mucous membrane had occurred during the oral inoculation and it is possible that the infection of the central nervous system was due entirely to invasion from the olfactory area.

Experiment A4-34.—

Apr. 13, 1943. Chimpanzee "Gene" was a small 20 pound male, about 3 years old, of a lively and inventive disposition.

Apr. 20. Under light chloroform anesthesia a stomach tube was passed and 15 cc. of human stool suspension (Kotter) was given without incident. While the animal was still in a somewhat stuporous condition an additional 5 cc. of stool was placed in the mouth and the animal's cheeks and lips were massaged until it was swallowed.

Apr. 21 and 22. Received 15 cc. of Kotter stool by stomach tube and 5 cc. by mouth as on Apr. 20. Two *rhesus* monkeys inoculated with the same material became paralyzed on Apr. 29.

Apr. 28. Stool obtained on this day produced paralytic poliomyelitis in 2 *rhesus* monkeys inoculated intranasally.

May 3. No unusual symptoms had been observed hitherto but on this day his rectal temperature was slightly elevated and the right knee jerk was difficult to obtain. The left knee jerk was quite active. No muscular weakness or other reflex abnormalities could be detected.

May 4. The rectal temperature reached 102°C. yesterday but today is 100°. The animal is listless and reflex differences in the legs are still present but there is no definite weakness.

May 5. Symptoms are unchanged. Lumbar puncture revealed about 400 small lymphocytes per cc. of cerebrospinal fluid.

May 11. Daily examinations have revealed no change in tendon reflexes and no additional clinical signs. The animal was bled under ether anesthesia and embalmed after tissues had been removed for virus assay. Stool obtained on this day produced paralytic poliomyelitis in a *rhesus* monkey inoculated intranasally.

Summary of Microscopic Findings.—Examination of the brain and spinal cord revealed that this chimpanzee had sustained a rather severe non-paralytic infection. Typical lesions of moderate to severe intensity were observed in the cervical and lumbar cord and were distributed in characteristic fashion in the brain (Table I; Fig. 5). Since lesions were not found in the olfactory bulbs, it is likely that the alimentary tract served as portal of entry but the precise area involved could not be determined.

Experiment A4-35.—

Apr. 13, 1943. Chimpanzee "Curley," a robust 32 pound female of about 4 years of age, was received from the dealer.

Apr. 20. Under light chloroform anesthesia a stomach tube was passed and 15 cc. of human stool suspension (Kotter) was given without incident. While the animal was still in a somewhat stuporous condition an additional 5 cc. of stool was placed in the mouth and the animal's lips and cheeks massaged until it was swallowed.

Apr. 21 and 22. Received 15 cc. of Kotter stool by stomach tube and 5 cc. by mouth as on Apr. 20. Two *rhesus* monkeys inoculated with the same material became paralyzed on Apr. 29.

Apr. 28 and May 14. Stool obtained on these days produced paralytic poliomyelitis in two *rhesus* monkeys inoculated intranasally.

May 18. No evidence of clinical poliomyelitis has been observed by daily examination thus far. Under ether anesthesia she was bled and embalmed after tissues were removed for virus assay.

Summary of Microscopic Findings.—Pathological findings in the central nervous system of this animal were scanty and somewhat atypical (Table I; Figs. 6 and 7). No lesions were found in the spinal cord. Perivascular lesions were found in the substance of the hindbrain. In the forebrain perivascular and focal infiltrative lesions were found only in the lateral thalamus (Fig. 6). Pathological changes in the left cerebellar hemisphere were more extensive

than are usually found and seemed to be disproportionate to the scanty involvement of the rest of the brain. Examination of complete serial sections in this region of the hindbrain and cerebellum revealed a small solitary granuloma in the white matter of the left cerebellar hemisphere associated with a cuffed vessel (Fig. 7). Although the chimpanzee was in robust health at the time of death, and no evidence of tuberculosis was seen on gross inspection in thoracic or abdominal viscera, it seemed possible that the granuloma was of tuberculous origin. It was, however, difficult to interpret the numerous cuffed vessels in the cerebellum at some distance from this lesion, as well as the foci of infiltration in the molecular layer of the cerebellum which were not dissimilar to those seen in poliomyelitis. Since the lesions in the thalamus and in the reticular formation of the hindbrain were remote from the cerebellar granuloma and comparable with those seen in typical poliomyelitis cases, it seemed possible that a mild poliomyelitis infection of the brain existed concurrently with the process which induced the granuloma formation. Moreover, in view of the fact that this animal was also shown to have virus in its stools 3 weeks after inoculation, it was presumed to be highly likely that the brainstem lesions represented a mild poliomyelitic infection.

Experiment A4-36.—

Apr. 10, 1943. Chimpanzee "Angel" was received from a showman. She was a robust female about 4 years of age.

Apr. 20. Under light chloroform anesthesia a stomach tube was passed and 15 cc. of human stool suspension (Kotter) was given without incident. While the animal was still somewhat stuporous, an additional 5 cc. of stool was placed in the mouth and the animal's lips and cheeks massaged until it was swallowed.

Apr. 21 and 22. Received 15 cc. of stool by stomach tube and 5 cc. by mouth as on Apr. 20. Two *rhesus* monkeys inoculated with the same material were paralyzed on Apr. 29.

Apr. 25. A slight temperature elevation (101.2°C.) was present today.

Apr. 27. Temperature normal. Cerebrospinal fluid was clear, contained one leucocyte per c.mm. and a trace of globulin. No reflex or motor changes were observed.

May 13. Daily examinations have revealed nothing suggestive of clinical poliomyelitis. Under chloroform anesthesia she was bled and embalmed after material was removed for virus assay. Stool obtained on this day produced paralytic poliomyelitis in an intranasally inoculated *rhesus* monkey.

Summary of Microscopic Findings.—This animal showed typical poliomyelitic lesions of moderate degree in the olfactory bulbs (Fig. 8), and relatively few other lesions, which, however, were scattered throughout the brain with the characteristic distribution of poliomyelitis (Table I). No lesions were found in the spinal cord. Although the lesions in the olfactory bulbs consisted of both perivascular and focal infiltration with some neuronal destruction, the lesions in the rest of the brain consisted only of definite perivascular infiltrations. Apparently in this animal contamination of the olfactory bulbs had occurred during the oral inoculation, and invasion of the brain had occurred from the olfactory area. Although few in number, the lesions in the brain were characteristic of poliomyelitis in nature and in distribution.

Experiment A4-47.—

May 21, 1943. Chimpanzee "Tina" was a robust 31 pound female about 3.5 years of age. Under chloroform anesthesia at the dealer's 15 cc. of blood was taken for serum.

June 25. Animal arrived at the laboratory in good condition.

June 28. Was given intraperitoneally 50 cc. of pooled hyperimmune anti-Kotter monkey serum.

June 29. Received 50 cc. of hyperimmune monkey serum (Kotter) intraperitoneally followed in about one-half hour by 15 cc. of human stool suspension (Kotter) by stomach tube and 5 cc. by mouth. Light chloroform anesthesia was used. *Rhesus* monkey A5-02 inoculated intranasally with the same stool suspension was paralyzed on July 7. Another *rhesus* control,

A5-03, inoculated intranasally with this material sustained a non-paralytic infection confirmed histologically.

June 30 and July 1. Received 35 cc. of serum intraperitoneally, followed by 20 cc. of Kotter stool under light chloroform anesthesia, as before.

July 20. Stool obtained on this day produced paralytic poliomyelitis in 2 *rhesus* monkeys inoculated intranasally.

July 29. Daily examination has revealed no signs of weakness, but 1° of fever was present on July 8 and during the period of July 13 to 15. Under chloroform and ether she was bled for serum and then exsanguinated, and autopsied. Stool obtained on this day produced non-paralytic poliomyelitis in a *rhesus* monkey inoculated intranasally. The diagnosis was made histologically.

Summary of Microscopic Findings.—Relatively few lesions were found in the brain and none in the spinal cord. In the brain the lesions consisted of definite perivascular infiltrations and a number of focal round cell infiltrations distributed in centers usually involved in poliomyelitis (Table I; Figs. 9 and 10). The olfactory bulbs were normal, suggesting invasion of the CNS from the alimentary tract. A small subpial caseous focus, probably representing a solitary tubercle, was found in the parietal cortex, associated with light perivascular cuffing of a neighboring vessel. Since no other lesions of this nature were found, it was concluded that the more generalized perivascular and focal infiltrations indicated in Table I probably resulted from a poliomyelitic infection.

Experiment A4-48.—

May 21, 1943. Chimpanzee "Toto" was a small, active 25 pound male about 3 years of age in good physical condition. Was bled for serum at the animal dealer's under chloroform anesthesia.

June 25. Was received from the dealer in good condition.

June 28. Was given intraperitoneally 50 cc. of pooled hyperimmune anti-Kotter monkey serum.

June 29. Received 50 cc. monkey hyperimmune serum (Kotter) intraperitoneally followed in about one-half hour by 15 cc. of human stool suspension (Kotter) by stomach tube and 5 cc. of stool by mouth. The stool was given under light chloroform anesthesia. *Rhesus* controls A5-02 and A5-03 subsequently suffered poliomyelitis attacks, as noted in case A4-47.

June 30 and July 1. Received 35 cc. of serum intraperitoneally, followed by 20 cc. of Kotter stool under light chloroform anesthesia, as before.

July 10. Has had a head cold since yesterday and today showed 1° of fever.

July 16. Was listless yesterday and today is very depressed and diarrheic, but there are no signs of weakness. Was placed on a diet of bread, milk, and apples, and was given carbarsone for intestinal parasites.

July 17. Appeared to be perfectly well.

July 20. Stool obtained today infected 1 of 4 *rhesus* monkeys inoculated intranasally (non-paralytic infection confirmed histologically).

July 29. Daily examinations have revealed no signs of weakness or any other symptoms suggestive of poliomyelitis. Under chloroform and ether blood was removed for serum and the animal was then exsanguinated, and autopsied. Stool obtained today failed to infect 2 *rhesus* monkeys inoculated intranasally.

Summary of Microscopic Findings.—Lesions in the brain in this case were quite similar in distribution to those in Experiment A4-47 but were more numerous and included, in addition, a few perivascular infiltrations in the olfactory bulbs (Figs. 12 to 14). No lesions were found in the spinal cord. The pathological picture in the brain was considered to be characteristic of a mild poliomyelitic infection, but the cuffed vessels in the olfactory bulbs were considered to be so few as to be an uncertain indication of olfactory invasion of virus.

Experiment A5-01.—

June 28, 1943. Chimpanzee "O'Toole" was a robust young 22 pound male about 3 years of age, who had been received 1 week ago and had been isolated until today. Blood was removed by venapuncture for serum and he was then given 50 cc. of pooled hyperimmune anti-Kotter monkey serum intraperitoneally. Following this he lay immobile on the cage floor for a few minutes but showed no further reaction.

June 29. Received 50 cc. of hyperimmune monkey serum intraperitoneally (Kotter) followed in a half-hour by 15 cc. of Kotter stool by stomach tube and 5 cc. of stool by mouth. Anesthesia was not used. *Rhesus* controls A5-02 and A5-03 subsequently had poliomyelitis infection as noted under Experiment A4-47.

June 30 and July 1. Received 35 cc. of convalescent serum intraperitoneally, followed in 30 minutes by 20 cc. of Kotter stool given as on June 29.

July 7. Has shown no symptoms suggestive of poliomyelitis but is listless and diarrheic and has been losing weight.

July 9. Was given 300 mg. carbarsone yesterday and was more active today. Was placed on a high caloric diet.

July 20. Stool obtained on this day produced paralytic poliomyelitis in an intranasally inoculated *rhesus* monkey. The diagnosis was confirmed histologically.

July 28. Daily examination has revealed no signs of weakness or other symptoms of poliomyelitis. Under chloroform and ether 50 cc. of blood was removed by cardiac puncture for serum, and the animal was then exsanguinated and autopsied.

Summary of Microscopic Findings.—The pathological picture in the CNS of this animal was of unusual interest (Table I). Typical cuffing and focal infiltration of light degree were found in the olfactory bulbs, indicating olfactory contamination during the oral inoculation (Fig. 11). The rest of the brain showed no lesions except for perivascular infiltration in the secondary olfactory centers, motor cortex, and midbrain tegmentum. These are centers characteristically involved after intranasal inoculation. The spinal cord contained no lesions. It was considered that the pathological picture in the CNS was a result of a mild poliomyelitic infection arrested at an early stage after olfactory invasion. This type of arrest of the progression of the pathological process down the brain stem after intranasal inoculation is quite comparable to that seen not infrequently in *rhesus* monkeys (4, 5).

History and Findings in Convalescent Chimpanzees

Experiment A3-91.—

Dec. 7, 1942. Chimpanzee "Caroline" was a small female about 3 years of age and in excellent physical condition. She was bled for serum at the dealer's office where she remained until Jan. 5, 1943.

Jan. 6, 1943. She was given 16 cc. of human stool suspension (Sudeck) by mouth. The material was taken willingly and was rolled around in the mouth a good deal before being swallowed. Two *rhesus* monkeys inoculated intranasally with this material became paralyzed on Jan. 24.

Jan. 7. Received 13 cc. of Sudeck stool by mouth.

Jan. 8. Received 8 cc. of Sudeck stool by mouth. The stool was taken without anesthesia on all 3 days.

Jan. 29 and Mar. 2. Stool obtained on these days produced paralytic poliomyelitis in intranasally inoculated *rhesus* monkeys.

May 24. The animal had shown no signs of clinical poliomyelitis, but since chimpanzee A3-92, which had been inoculated at the same time, was found to have had rather extensive non-paralytic infection, it was thought that A3-91 might have had a similar non-paralytic infection. It was hoped that despite the long period which had elapsed since inoculation,

there would still be lesions in the nervous system since the isolation of virus from stools of Jan. 29 and Feb. 5 had left little doubt that Caroline had had a non-paralytic attack.

Summary of Microscopic Findings.—Although 5 months had elapsed between the time of inoculation and the time of death of this animal, residual lesions were present in the brain and cord indicating that a non-paralytic infection had occurred. The lesions were very sparse and consisted of definite perivascular infiltration, but these were distributed in characteristic fashion in the brain, as well as being present in the spinal cord. The olfactory bulbs contained perivascular and focal infiltrative lesions which indicated that the olfactory area had been accidentally contaminated during the oral inoculation. Invasion of the nervous system had probably occurred by this route.

Experiment A5-27.—

Sept. 13, 1943. Chimpanzee "Bobo," a small male weighing 25.5 pounds and in good condition, was received from the animal dealer. Tuberculin test was negative.

Oct. 26. The animal has gained weight. Without anesthesia 5 cc. of 10 per cent cord suspension of tested virulence (Kotter strain) was dripped into the mouth with a hypodermic syringe over a period of several minutes. All the inoculum was taken without resistance, mulled around in the mouth, swallowed, and retained. Stool specimens were saved daily.

Oct. 29 and 31. Stool specimens produced paralytic poliomyelitis in intranasally inoculated *rhesus* monkeys.

Nov. 5 to 11. During this period has had 1° of fever. Lumbar puncture on Nov. 11 yielded cerebrospinal fluid without abnormality. Stools obtained on Nov. 2, 4, 6, 11, and 16 and on Dec. 3, produced paralytic poliomyelitis in intranasally inoculated *rhesus* monkeys.

Feb. 11, 1944. Daily examination has hitherto revealed no signs suggestive of poliomyelitis. Under light chloroform anesthesia he was reinoculated with 1.25 cc. of 10 per cent Kotter cord suspension intranasally. The inoculum was part of the same pool as that used previously.

Mar. 2. 1° of fever was present today but spinal fluid was found to be normal. A hacking cough was present and sputum was found to contain many pus cells, a predominance of Gram-positive cocci, and no acid-fast organisms. Tuberculosis was suspected, but sulfathiazole therapy was instituted and continued for a week.

Mar. 21. Is alert and active but continues to have a chronic cough. He was reinoculated with 5 cc. of 10 per cent cord suspension intraorally without anesthesia. The material was derived from the same pool of cord suspension previously used.

Apr. 21. Roentgenogram of the chest revealed a heavy shadow involving the lower right lobe of the lung.

May 8. Tuberculin test has been negative. Animal has had occasional fever of 1°. Today a right facial paralysis involving upper and lower facial muscles was observed. There are no other signs of weakness or reflex changes. Spinal fluid was essentially normal.

May 10. No change in clinical signs today. Under ether anesthesia the abdomen was opened and extensive miliary tuberculosis was found involving liver, spleen, peritoneum, and intestinal walls. The animal was then embalmed and tuberculous pneumonia was found to have been present. The central nervous system and peripheral ganglia were removed for histological studies.

Summary of Microscopic Findings.—The brain and spinal cord of this animal were carefully examined but no lesions of any sort were found. The meninges were normal in appearance. The right Gasserian ganglion was found to contain a rather large tubercle but no lesions suggestive of poliomyelitis. Similarly the stellate ganglia contained numerous small tubercles but none of the small infiltrative foci seen in autonomic ganglia of other inoculated chimpanzees were present. The terminal right facial paralysis was thought to be due to a tuberculous involvement of the facial nerve, similar to that involving the trigeminal nerve.

In view of the length of the period (6.5 months) which elapsed between the time of first inoculation and the time of death it is conceivable that lesions due to a mild non-paralytic infection of the central nervous system following the first inoculation had cleared up. The absence of acute lesions in the nervous system, and the absence of virus in the stools after the second and third inoculations, can have no clear cut interpretation, since reinfection may have been prevented by immunity resulting from the first infection or by the terminal tuberculous infection.

Experiment A1-74.—

Dec. 6, 1940. Chimpanzee "Bozette" had been in the laboratory since June and was a healthy female of about 4.5 years of age and weighing 22 pounds. Under chloroform-ether a trephine opening was made in the right frontal region and 0.5 cc. of cord suspension of chimpanzee A83 was inoculated into the right motor cortex. The cord suspension was known to produce poliomyelitis in *rhesus* monkeys. Postoperative recovery was uneventful. Stool obtained on this day failed to produce poliomyelitis in two intranasally inoculated *rhesus* monkeys.

Dec. 10. Fever of 4° was present and continued until Dec. 13.

Dec. 12. Left arm was weak and lumbar puncture yielded spinal fluid containing 150 cells per c.mm., with 80 per cent lymphocytes.

Dec. 14. Left arm is now practically useless and hangs limply at the side. Tendon reflexes are absent and grasp is feeble. The right arm and lower right facial muscles also show moderate weakness.

Dec. 16. Paralysis has progressed to the point where the left arm is not moved at all, right arm has about 20 per cent of normal function, and the legs have about 50 per cent of normal function. There appears to be some difficulty in swallowing. Stool obtained on this day failed to produce poliomyelitis in 2 *rhesus* monkeys inoculated intranasally.

Dec. 18. The animal is more active and aggressive and the right arm is much stronger than before.

Dec. 23. Has been improving steadily since the last note. Now uses all extremities, feeds herself without difficulty, and climbs carefully about the cage.

Feb. 7, 1941. The animal has had a persistent cough during the past month and has lost 2 pounds of weight during that period. Râles and friction rubs have been noted in examination of the left side of the chest and tuberculosis was suspected. The right arm is about 40 per cent functional, the left arm about 15 per cent functional with severe atrophy present, and the legs are about 50 per cent functional. Under nembutal the animal was inoculated intranasally with 20 per cent cord suspension of A83. 0.5 cc. was instilled into each nostril over a period of 15 minutes.

Feb. 8. Reinoculated intranasally as on Feb. 7.

Feb. 17. Stool failed to infect 2 *rhesus* monkeys inoculated intranasally.

Feb. 20. The animal has been getting progressively debilitated but no additional paralysis could be demonstrated. She was, therefore, etherized, exsanguinated, and autopsied.

Summary of Microscopic Findings.—Although 70 days elapsed between the date of initial paralysis and the time of death, numerous chronic lesions of poliomyelitis were still present in the brain, consisting of perivascular cuffing and focal glial accumulations. The gray matter in the spinal cord in lumbar and cervical regions showed perivascular infiltrations of round cells and considerable diffuse gliosis as well as marked decrease of anterior horn cells. These lesions appeared to be old. The olfactory bulbs showed typical fresh lesions of poliomyelitis consisting of perivascular cuffing and focal infiltrations of lymphocytes. These findings indicate that this animal had sustained a second attack of poliomyelitis in which the pathological changes had apparently not extended down into the previously invaded brain stem and spinal cord.

Experiment A3-58.—

Sept. 2, 1942. Chimpanzee "Cilly" has been in the laboratory for 4 months but has been in isolation since arrival. She is in excellent condition, and weighs about 30 pounds. Under light chloroform anesthesia she received 20 cc. of human stool suspension (Sudeck) by mouth.

Sept. 3. and 4. On each of these days 20 cc. of Sudeck stool was given by mouth without anesthesia. Control *rhesus* monkey A3-69 inoculated intranasally became paralyzed on Sept. 13.

Sept. 17 and Oct. 5. Stools obtained on these days each were inoculated intranasally into 3 *rhesus* monkeys, which failed to acquire poliomyelitic infection.

Apr. 15, 1943. No signs suggestive of poliomyelitis have been noted although the animal has been under continuous observation. While being chloroformed for additional inoculation, she died suddenly. She was embalmed and autopsied.

Summary of Microscopic Findings.—Although 7.5 months had elapsed between the time of inoculation and the time of death, residual lesions, probably of poliomyelitis, were found distributed in characteristic fashion in the brain. These lesions consisted entirely of perivascular cuffing and similar lesions were found in the lumbar cord. Some sections of lumbar cord showed evidence of loss of anterior horn cells. This animal had apparently sustained a non-paralytic attack of poliomyelitis with sufficient pathological involvement so that residual lesions were present after about 7 months.

Findings in Normal Chimpanzees

Experiment A1-00.—

Jan. 12, 1940. Chimpanzee "Rollo" was a young male about 2.5 years of age weighing 18 pounds when received from the dealer.

Jan. 18. Under nembutal anesthesia a frontal craniotomy was done, frontal poles of the brain retracted, and the olfactory tracts cut. During the operation the animal stopped breathing but respiration returned to normal after compressed air was given through a nasal tube. Following the operation the animal appeared to be in good condition and was given 60 cc. of human stool suspension by stomach tube. While still on the table respiration ceased again but was reestablished as before.

Jan. 19. At 9 a. m., after several spells of hiccoughing and vomiting, the animal expired. He was immediately perfused and autopsied. The lungs contained a number of consolidated areas and the main bronchi contained aspirated fecal material. The cranial cavity showed no evidence of excessive bleeding.

Summary of Microscopic Findings.—Since this animal had died less than a day after inoculation it was considered useful as a normal control. Examination of the brain, spinal cord, and peripheral ganglia revealed no lesions of any kind.

Experiment A1-01.—

Jan. 9, 1940. Chimpanzee "Carlo" was a young male about 3 years old who failed to survive an intracranial operation in another department. Death was due to subarachnoid hemorrhage in the medulla oblongata. He was perfused immediately after death and the CNS and peripheral ganglia were removed in order to be used as histological controls.

Summary of Microscopic Findings.—The brain and peripheral ganglia contained no lesions which could be considered characteristic of poliomyelitis.

Experiment A1-73.—

Dec. 1, 1940. Chimpanzee "Verma" was a young female about 3 years of age who had been in the laboratory since Nov. 22, 1940. She had never been inoculated and on this day developed acute respiratory distress and died within a few hours. She was perfused immediately

after death and the brain and peripheral ganglia were removed to serve as histological controls. The cause of death was apparently a diffuse bronchopneumonia.

Summary of Microscopic Findings.—No lesions of any sort were found in sections of the brain and peripheral ganglia.

Experiment A8-07.—

June, 1940. This young chimpanzee was received from a dealer as a gift since it had osteomyelitis of the jaw. Its death occurred within 24 hours after arrival, apparently largely due to starvation. The animal was perfused several hours after death and only the brain was saved.

Summary of Microscopic Findings.—No lesions of any sort were found in the brain.

Non-Paralytic Attack Followed by Paralytic Second Attack

Experiment A48.—

In reviewing our total experience with both paralytic and non-paralytic chimpanzees we have been impressed with the uniqueness of the pathological picture presented by chimpanzee A48. This animal was described by us in previous reports in which the localization of lesions in that part of the brain associated with the portal of entry was interpreted as an instance of early arrest of the pathological process (see Table I). In one of these reports (4) four other instances of early arrest of the pathological process near the portal of entry in the brain were cited, 3 in intranasally inoculated *rhesus* monkeys, and 1 in an intranasally inoculated chimpanzee which was suffering from advanced pulmonary tuberculosis at the time of inoculation (A1-75). Since then, 8 other similar cases have come to our attention in intranasally inoculated *rhesus* monkeys, 3 of which had typical poliomyelitis lesions restricted exclusively to the olfactory bulbs (A1-46, A8-04, A8-35). These examples stand in contrast with chimpanzee A48 in which the portal of entry after oral feeding of potent human stool appeared to be the trigeminal nerve, and in which acute lesions were found only in the trigeminal ganglia and in regions of the hindbrain close to the entrance of the trigeminal nerve. A topographic restriction of lesions to such an extent in the central nervous system has not occurred in our chimpanzees, except A1-75 in which advanced pulmonary tuberculosis and extreme debility existed (Table I). Moreover, our increasing awareness of the importance of non-paralytic infections in chimpanzees prompted us to reexamine A48 for evidence of a previous unrecognized attack of non-paralytic poliomyelitis following a stomach tube inoculation of potent human poliomyelitis stool 8 months before the successful oral inoculation. That A48 experienced a second attack of poliomyelitis now appears highly probable, as will be shown. Moreover, the early arrest of the pathological process during the second paralytic attack, with very little spread of lesions in a rather highly susceptible region of the central nervous system appears to be the result of partial resistance conferred by a previous non-paralytic attack. The protocol of this chimpanzee is of sufficient importance to be resummarized here.

Oct. 16, 1939. A 4 year old male chimpanzee, "Bozo," in robust health, was anesthetized with nembutal to the point where a stomach tube could be passed without eliciting a gag reflex. By this means he was given 25 cc. of the supernatant fluid from a pool of 6 different potent human poliomyelitic stools (Baltimore, 1939). There was no regurgitation and the tube was washed before removal.

Oct. 22. Temperature elevated from a baseline of 101–102° to 104.4°F. The animal appeared perfectly well and the temperature was normal the next day.

Oct. 26, 27, 28. Received 25, 25 and 20 cc. of the same stool pool on 3 days as indicated, by stomach tube. The last two inoculations were done without anesthesia and on the final one the tube was withdrawn before the entire inoculum had gone in, because the tube became plugged when the animal attempted to regurgitate.

Nov. 16 and 17. Temperature up from a baseline of 101 to 103.3°F.

Nov. 27. Temperature which had been normal since Nov. 17 reached 102.6° today. Slight nasal congestion.

Daily temperatures were maintained until Jan. 2, 1940, without further change. At no time did the animal show any clinical signs of poliomyelitis, other than fever about 3 weeks after the inoculation.

June 10, 11, 12, 1940. Under chloroform anesthesia he received 2 cc. of stool pool by mouth on each day indicated above. The pool was the same as that used on Oct. 16, 1939, and had been preserved at −78°C. Half the dose was placed in each cheek, which was gently massaged from without to simulate facial movement. At the same time a *rhesus* control, A1-49, was inoculated intranasally, along with 2 *cynomolgus* monkeys, A1-43 and A1-44, which received 9 cc. of stool each by stomach tube. The *cynomolgi* at no time showed any signs of poliomyelitis, but the *rhesus* was paralyzed on the 9th day.

July 9. Temperature rose from a baseline of 101 to 103°F. Stool obtained and inoculated intranasally into a *rhesus* monkey, A1-62, which showed no clinical signs of poliomyelitis, although non-paralytic poliomyelitis was not excluded in this animal.

July 10. Temperature 106°F. Animal listless, but showed no other abnormalities.

July 11. Temperature down to normal. Animal is again active. Lumbar puncture showed clear spinal fluid which clotted immediately. A smear from the clot showed few erythrocytes, and large numbers of lymphocytes. One granulocyte (an eosinophil) was seen. At 4 p.m. ptosis of the left eyelid was noted. Stool inoculated into *rhesus* Al-70 produced no clinical or histological reaction (10 intranasal inoculations).

July 12. Ptosis quite marked; animal seen to rub eye frequently.

July 13. Ptosis unchanged. Left lower lip was drawn over teeth when animal yawned or grimaced. No other abnormalities.

July 15. Ptosis less marked, but lip unchanged. Animal anesthetized, bled, and various tissues removed for virus studies. These resulted as follows: olfactory area of nasal mucosa negative in *rhesus* A2-14; tonsil negative in *rhesus* A2-12 and A2-13; walls of small intestine negative in *rhesus* A2-17 and A2-18; large intestine negative in A2-15 and A2-16; stool negative in *rhesus* A1-63, and questionably positive microscopically in *rhesus* A1-71 (all inoculations done as 10 successive daily intranasal instillations).

Summary of Microscopic Findings.—There was a diffuse meningitis and a few local accumulations of lymphocytes were present in the pia-arachnoid of the orbital gyri. Similarly, the olfactory bulbs showed infiltration of lymphocytes around the fila of the olfactory nerve where they pass from the cribriform plate through the subarachnoid space to enter the bulb. There was also perivascular cuffing of some of the vessels which adjoin the fila and penetrate the outermost layer of the bulb. No evidence of actual invasion of the olfactory bulbs could be seen. There was no destruction of mitral cells, no glial foci, or perivascular infiltration in any portion of the bulbs deeper than the outer layer of olfactory nerve fibers. No other lesions

were present rostral to the medulla. Reaction was first encountered caudally at the level of the entrance of the fifth nerve and was confined almost exclusively to the left side. Perivascular cuffing and focal infiltrations were found in the nucleus sensibilis and the nucleus of the spinal tract of the left fifth nerve. There was cuffing in the sensory nucleus of the ninth and tenth nerves on the left. Cuffing, lymphocytic infiltration, and neuronophagia were present in the left facial nucleus. The right facial nucleus and right motor nucleus of the fifth nerve showed a little infiltration and cuffing, respectively. There was a lightly cuffed vessel in the right hypoglossal nucleus and one in the right inferior olive. Heavy neuronophagia and lymphocytic infiltrations were found in the left Gasserian ganglion while the right ganglion contained one small lymphocytic focus. Two small cuffed vessels were found in the left vagus sheath near the medulla. The right superior cervical ganglion contained a small area of infiltration and cuffing, while the celiac ganglia showed a few small areas of infiltration and questionable cuffing. The significance of these slight changes in the sympathetic ganglia is very doubtful. No other lesions were found in the following tissues: ciliary, sphenopalatine, geniculate, nodose, jugular, and submaxillary ganglia, or sympathetic chains. The salivary glands showed accumulations of lymphocytes of doubtful significance. Despite the presence of many nematode cysts and erosions in the mucosa of the colon, no abnormalities were seen in the cells of Auerbach's and Meissner's plexuses of the jejunum, ileum, colon, and rectum.

The findings in the spinal cord were most interesting. Initially, serial sections of blocks taken at C_1, C_4, C_7, T_2, T_4, T_8, T_{10}, L_1, L_3, L_5, L_6, and L_7 had revealed no lesions except a single vessel at C_7 showing perivascular lymphocytic infiltration, and a sparsity of cells in the anterior horns of C_4 which was not considered significant at the time. Recent complete serial sections of segments C_5, C_6, C_8, T_1, and S_1, however, have demonstrated an average deficit of anterior horn cells of almost 60 per cent on the right side in segments C_5 and C_6 only, with some sections showing almost complete obliteration of motoneurons, and replacement gliosis (Fig. 4). No acute inflammatory lesions were seen at these levels, so that the cord lesion is best explained as a chronic one dating back to the first inoculation of this animal. The lesions in the brain, and especially the pathological picture in the motor nucleus of the left facial nerve, are in marked contrast, and obviously represent those of an acute infection (see Howe and Bodian, 6; Plate 15). The segmental localization of the severe cord lesions of the first attack demonstrate again that in non-paralytic poliomyelitis an extensive histological survey of the cord must be made before it can be considered certainly negative, since at a distance of 1 or 2 mm. from a region of severe change, the cord sections may show no changes whatever (4).

In brief, this unusual case suggests that following a non-paralytic attack in which the virus is probably widespread in the brain, (as is clear from the analysis of the non-paralytic chimpanzees killed in the acute stage), all the natural portals are not closed to subsequent invasion, but such invasion may be modified and restricted to a considerable extent. Apparently at least a partial acquired resistance, possibly non-specific as to strain, is responsible for this effect.

DISCUSSION

There is now abundant evidence that in typical cases of poliomyelitis in man (15, 16), and in monkeys (17, 18) the distribution of virus in the central nervous system parallels the distribution of the characteristic neuronal and infiltrative lesions. The pathological pattern has been further shown to be essentially

comparable in monkeys, chimpanzees, and in man, in paralytic poliomyelitis attacks (6). Moreover, as we have previously emphasized, the definitive distribution of lesions in the brain in paralytic individuals is so characteristic with respect to the sparing of certain refractory centers, that a diagnosis of poliomyelitis can be made from a histopathological study of the brain alone. Although the characteristic perivascular and focal infiltrations, and the neuronal lesions, are not specific for poliomyelitis and occur in other neurotropic virus diseases, the pattern of distribution of such lesions in the brain is specific and pathognomonic in paralytic poliomyelitis. We have also shown that although this distribution of cerebral involvement is invariably present in animals with cord damage, there are exceptional instances in which, after intranasal inoculation in *rhesus* monkeys, the full pattern of cerebral lesions can develop with subsequent arrest of the pathological process before cord involvement occurs (4, 5). In other non-paralytic infections, however, as also reported by Kling (8) and by Sabin and Ward (7), cord lesions may be abundantly present but too scattered to produce clinically apparent paralysis.

In addition to revealing these variations in the pathological picture occurring in non-paralytic attacks, our early experience with *rhesus* monkeys inoculated intranasally with human stool suspensions, had produced paralytic poliomyelitis in which the cerebral lesions, although distributed in characteristic centers, were few in number, small, and chiefly composed of perivascular infiltrations (Bodian and Howe, 5, Table I). Such monkeys, except for pathognomonic cord involvement, seem to parallel some of our non-paralytic chimpanzee cases, in which the cerebral lesions, although distributed in the characteristic pattern for poliomyelitis cases, were quite light. In most of these animals, cord lesions were not found, but the presence of virus in the stools at periods from 3 to almost 8 weeks following inoculation appears to establish the existence of poliomyelitis (Table I). Although virus was not recovered from the stools of 2 chimpanzees in which a pathological diagnosis of poliomyelitis was made, it is of considerable interest and importance that no chimpanzee in which virus was present in the stools failed to show scattered cerebral lesions in centers of established susceptibility during the acute stage (7 cases—Table I). To test further the significance of the mild cerebral lesions in inoculated non-paralytic chimpanzees, we have examined serial sections of the brains of 4 chimpanzees which were never inoculated and, as far as known, had had no previous contact with poliomyelitis virus (see Table I). These brains were entirely free of lesions, except for a single focus of perivascular round-cell infiltration in the pyriform cortex of 1 animal. Since these control chimpanzees were about the same age as the inoculated animals, and 2 of them had died 1 day after intracranial operation, we have concluded that the cerebral lesions seen in our "non-paralytic" chimpanzees were not accidental findings.

On the basis of this evidence it is necessary to assume that, since there is

reason to believe that the disease in man and in chimpanzees is similar, *the presence of virus in stools of symptomless individuals may be associated with cerebral lesions*, distributed throughout susceptible centers. Although such lesions may be light, their presence indicates the action of virus on the central nervous system with the possibility of production of local acquired resistance, as well as humoral antibodies. This leads us to the concept that a systemic or peripheral type of inapparent poliomyelitis, with virus restricted to peripheral tissues and ganglia, and absent in the central nervous system, may be rare or non-existent. Although this can never be subjected to critical proof in man, our chimpanzee experience gives one no reason to suppose that a purely systemic form of poliomyelitis exists.

Although our experiments demonstrate the action of virus on the central nervous system during inapparent poliomyelitic infections, as shown by the presence of lesions, the rôle of such virus action in determining resistance to subsequent reinfection is by no means clear. In considering the question of resistance there are at least two types of factors which must be distinguished. First, are those which are independent of previous infection or contact with the antigen, and which underlie the variability in degree of susceptibility of animals with no known previous virus contact. These factors, which include differential species and tissue susceptibility (6, 12), constitutional variables such as age and nutrition, and dosage, are particularly well shown in action in determining the wide frequency distribution of degree of pathological change in primary non-paralytic infections[2] (5). Secondly, there are those acquired factors which result from exposure to the virus, such as local resistance and humoral immunity, all of which may be superimposed in varying degrees. Some years ago (6, 19), we showed that animals which were still susceptible to second attacks with homologous virus had acquired a local resistance of the central nervous system as the result of their first attack. In this situation second invasions of virus apparently did not take place in regions which had previously been infected. While we do not know the relationship of this type of local resistance to humoral immunity, it seems apparent that it was sufficient to arrest the progress of virus when humoral factors were powerless to prevent initial invasion. What relation this phenomenon may have to resistance in natural infections one cannot say at present. Moreover, if the pathological reaction in a non-paralytic attack is an indicator of the degree of subsequent acquired local resistance to reinfection, the extent of protection afforded by such an attack to even homologous virus must be variable because of the wide variation in the extent of lesion formation in non-paralytic infections.

[2] Non-paralytic infections, it must be assumed, come closest to representing the result of infectious contact of the host with virus at the level of the "minimal infective dose."

Since the lesions in several of our non-paralytic chimpanzees were few, and scattered in the brain, it is possible that only a partial local resistance to subsequent infection with homologous virus could have been induced. On the other hand, it is also possible that visible lesions in the central nervous system give only a partial picture of the extent of virus reaction with tissue. One may speculate, for example, that concentrations of virus too small to detect by passage or lesion formation in "silent" areas of the central nervous system, or infection with strains of high antigenicity and low pathological potency, may also modify some nerve cells in the direction of increased resistance. Whatever interpretation may be placed on these findings, it seems clear from epidemiological studies that inapparent infections must play a rôle in the increased resistance of humans to paralytic poliomyelitis with increasing age, and that previous central nervous system involvement probably has its share in this resistance. Further investigation is necessary for the elucidation of the mechanisms involved.

It must also be recalled that some of our chimpanzees showed that non-paralytic individuals with mild symptoms of poliomyelitis (A4-34) or without symptoms (A3-92), but with virus in the stools, may exhibit a full-blown pathological picture of poliomyelitis in the brain and in the spinal cord. Such individuals might be expected to have relatively solid resistance, at least, to subsequent reinfection with homologous virus, but this remains to be proven critically.

SUMMARY

1. Thirteen cases of non-paralytic poliomyelitis infection in chimpanzees are described. Nine of these animals were excreting virus in their stools at periods of from 3 days to 8 weeks following inoculation.

2. All animals killed during the acute stage showed lesions in the brain distributed in centers usually involved in, and compatible with the presence of, poliomyelitic infection. In 2 chimpanzees typical cord lesions were also present. No lesions were found in the brains of 4 control chimpanzees which had had no virus contact as far as known. The occurrence of a purely systemic or peripheral form of poliomyelitis, without lesions in the central nervous system, has thus not been established.

3. Four instances of arrest of the pathological process near the portal of entry into the brain, indicating partial resistance, are included in this series. One was a chimpanzee inoculated intranasally (A1-75) who had severe tuberculosis at the time of inoculation. The second was an animal convalescent after intracerebral inoculation (A1-74), who sustained a second infection limited to the olfactory bulbs when inoculated intranasally 2 months later with homologous virus. The third (A5-01) was inoculated orally with human stool, but

contamination of the olfactory area resulted with infection of the olfactory bulbs and of the forebrain; virus was present in the stools of this animal. The fourth chimpanzee (A48) had suffered an initial non-paralytic attack after stomach tube inoculation, followed by a second attack about 9 months later after oral inoculation with part of the same virus-containing pool (human stools). The second attack consisted of a facial paralysis, with arrest of the pathological process near the facial nucleus.

4. Although cerebral lesions were light in some of the non-paralytic and inapparent infections, their presence in all indicates the action of virus on the central nervous system with the possibility of production of at least partial local resistance. It is not unreasonable to assume that this may occur in inapparent human cases, although the point is, of course, not susceptible to critical proof in man.

5. The degree of severity of pathological involvement in non-paralytic cases varies from a fully developed distribution of lesions in brain and spinal cord in some chimpanzees, to mild and scattered lesions in the brains of others. This suggests that if the extent of pathological reaction is an indicator of subsequent local resistance to reinfection, the degree of protection afforded by a non-paralytic attack of poliomyelitis to even homologous virus must be variable.

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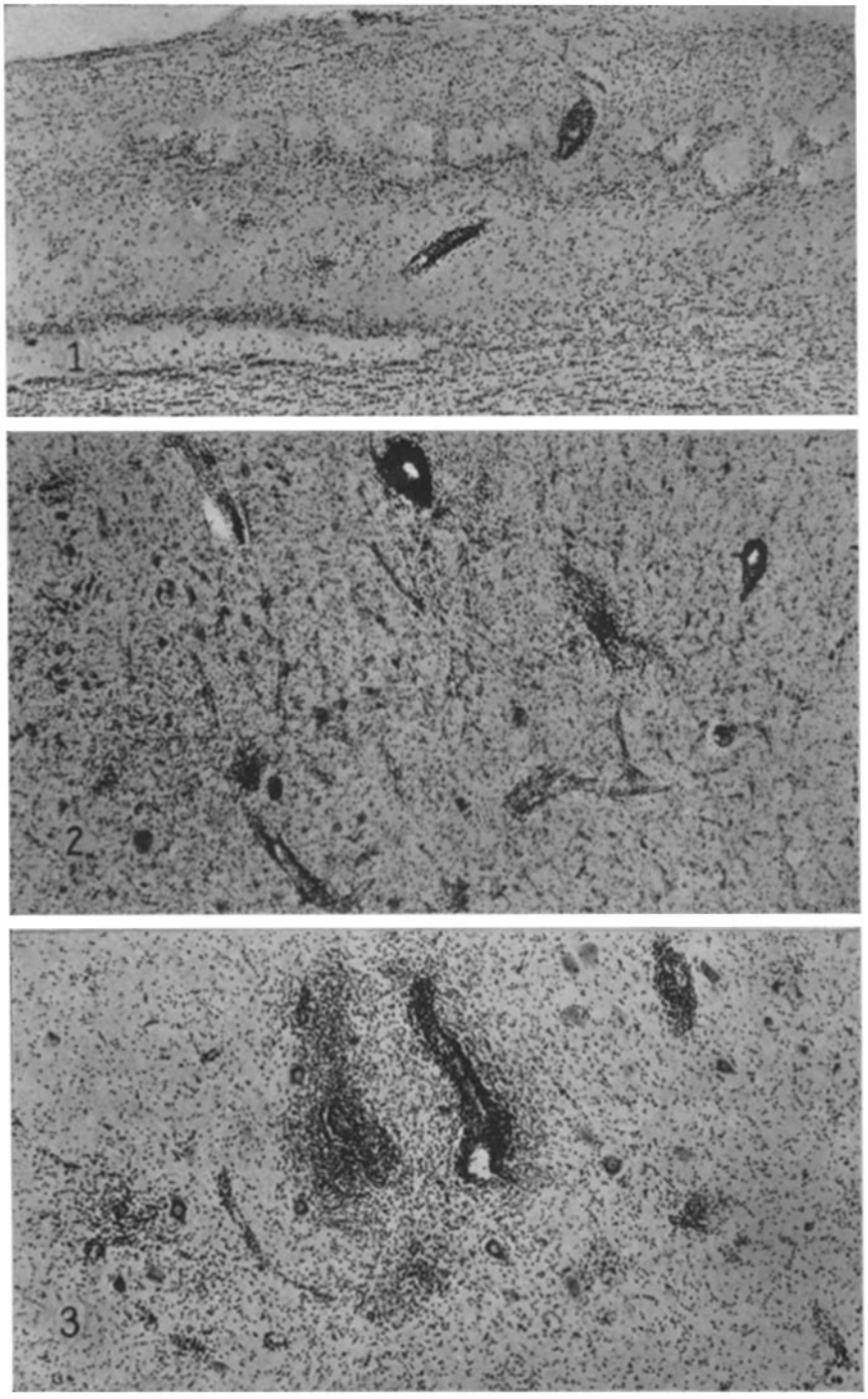
EXPLANATION OF PLATES

PLATE 15

FIG. 1. Olfactory bulbs of chimpanzee A3-92, with non-paralytic infection, showing poliomyelitic lesions. × 60.

FIG. 2. Poliomyelitic lesions in reticular formation of medulla oblongata of chimpanzee A3-92. × 60.

FIG. 3. Poliomyelitic lesions in anterior horn of spinal cord of chimpanzee A3-92. × 60.

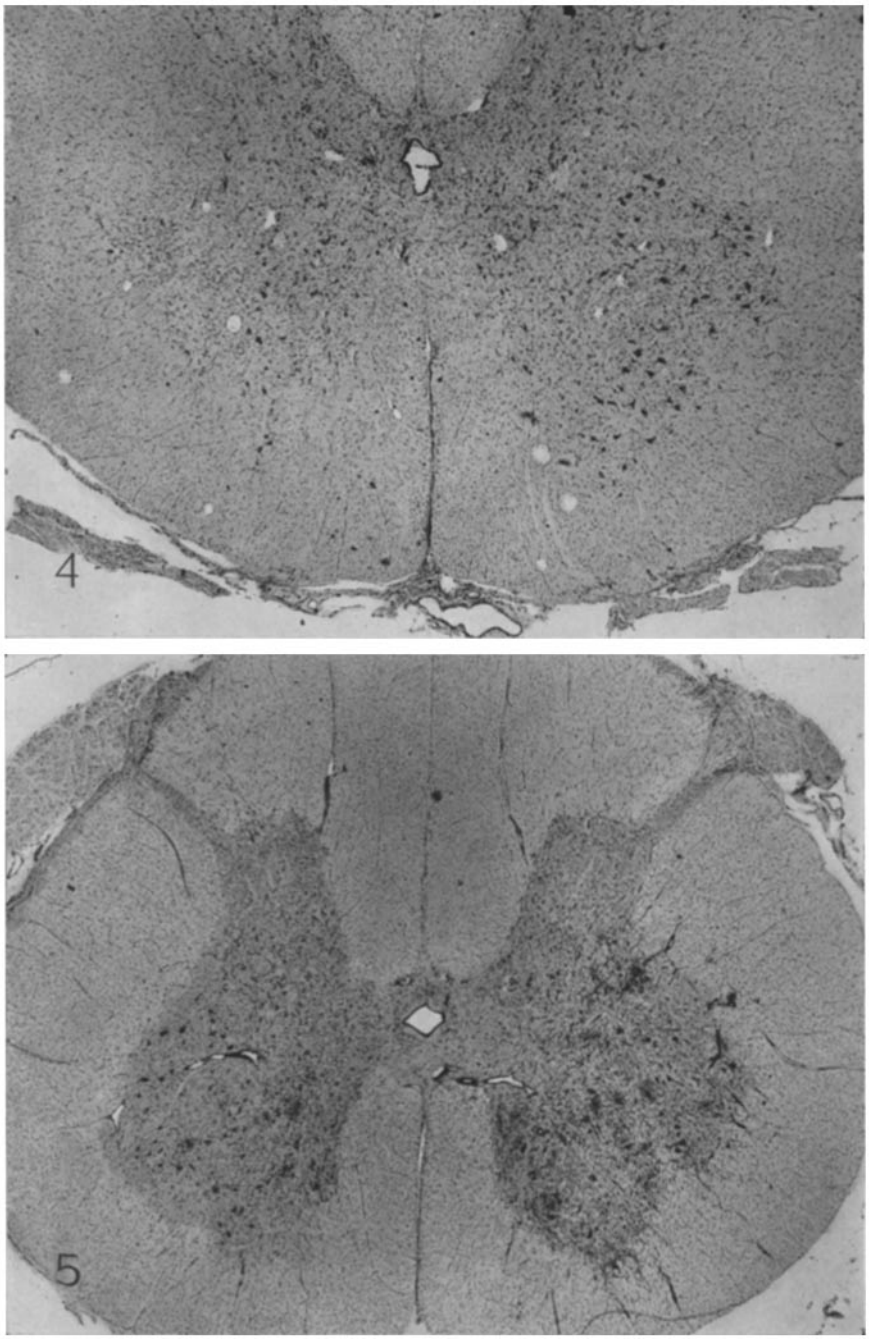


(Bodian and Howe: Non-paralytic poliomyelitis in chimpanzee)

PLATE 16

FIG. 4. Sixth cervical segment of spinal cord of chimpanzee A48, showing loss of anterior horn cells and replacement gliosis on right side (apparent left), apparently due to non-paralytic poliomyelitis, suffered 9 months previously. × 20. Lesions of acute stage of second attack are shown in Howe and Bodian (6, Plate 15).

FIG. 5. Spinal cord of chimpanzee A4-34, with non-paralytic poliomyelitis in acute stage, showing severe poliomyelitic lesions in left anterior horn (apparent right), although no detectable paralysis resulted. × 15.



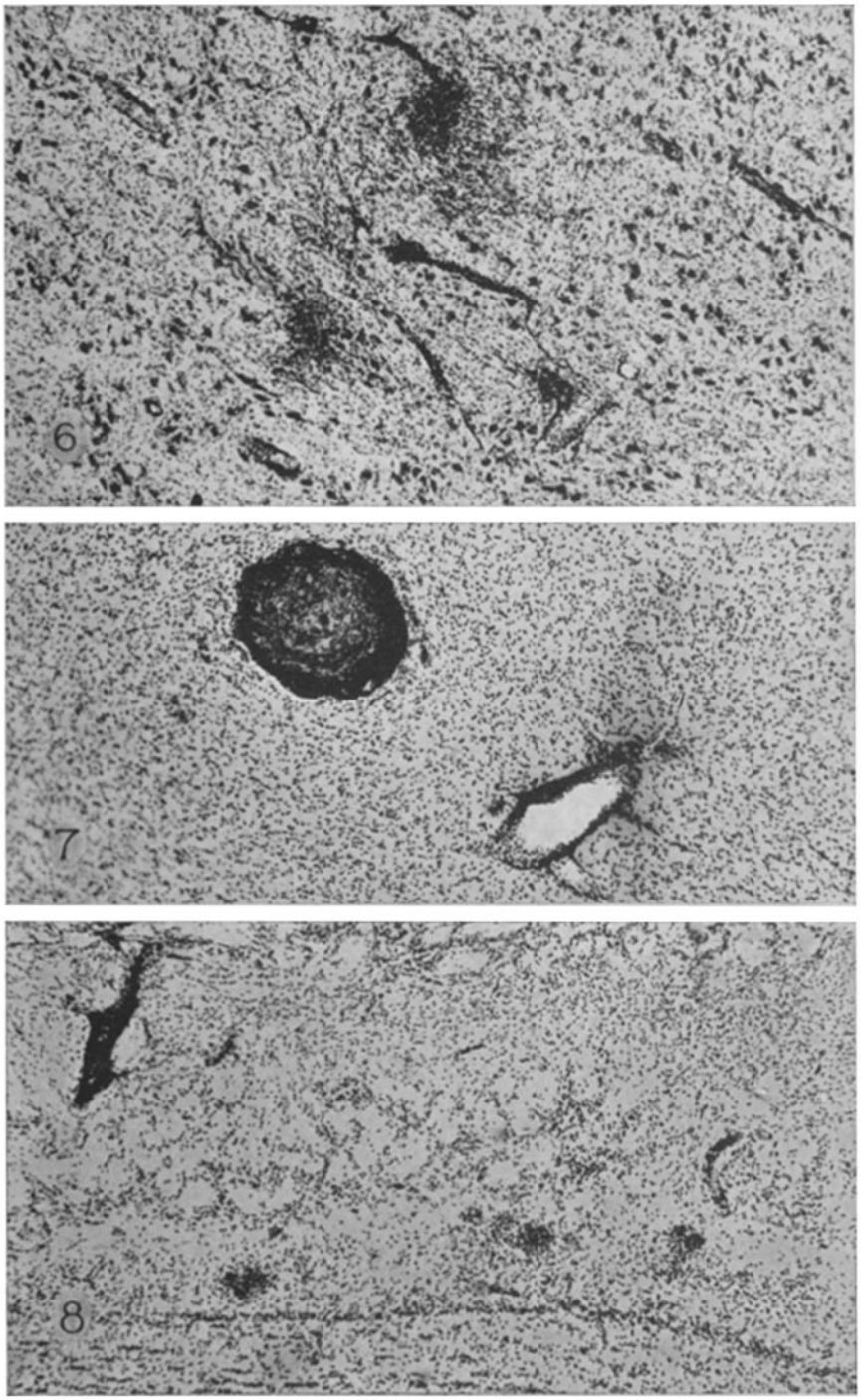
(Bodian and Howe: Non-paralytic poliomyelitis in chimpanzee)

PLATE 17

FIG. 6. Thalamus of chimpanzee A4-35, with non-paralytic poliomyelitis, showing lesions characteristic of poliomyelitis. × 60.

FIG. 7. White matter of cerebellar hemisphere of chimpanzee A4-35, showing granulomatous lesion with central giant cells and neighboring perivascular infiltration. The solitary granuloma seems not to bear any relation to scattered lesions in the brain characteristic of poliomyelitis in nature and in distribution. × 60.

FIG. 8. Olfactory bulb of chimpanzee A4-36, with non-paralytic poliomyelitis, showing numerous typical lesions. × 60.



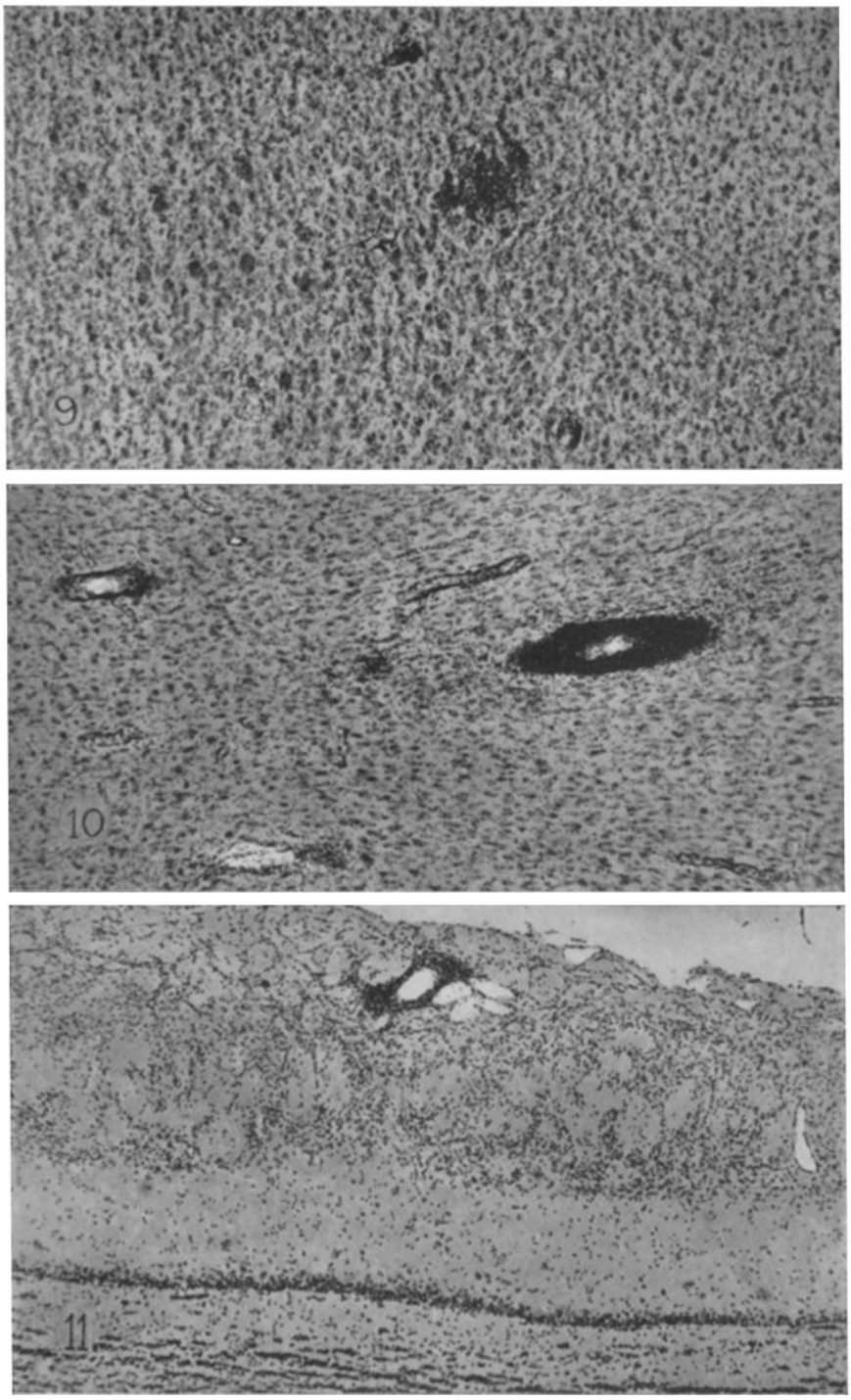
(Bodian and Howe: Non-paralytic poliomyelitis in chimpanzee)

PLATE 18

FIG. 9. Motor cortex (area 4 of Brodmann) of chimpanzee A4-47, with non-paralytic poliomyelitis, showing characteristic focal and perivascular mesodermal-glial infiltrations. × 60.

FIG. 10. Frontal cortex of chimpanzee A4-47, showing heavy perivascular infiltration, and focal round-cell lesion. × 60.

FIG. 11. Olfactory bulb of chimpanzee A5-01, with non-paralytic poliomyelitis showing cuffed vessel in outer layers, possibly poliomyelitic in origin. Lesions were not found in the deeper layers of the olfactory bulbs. × 60.



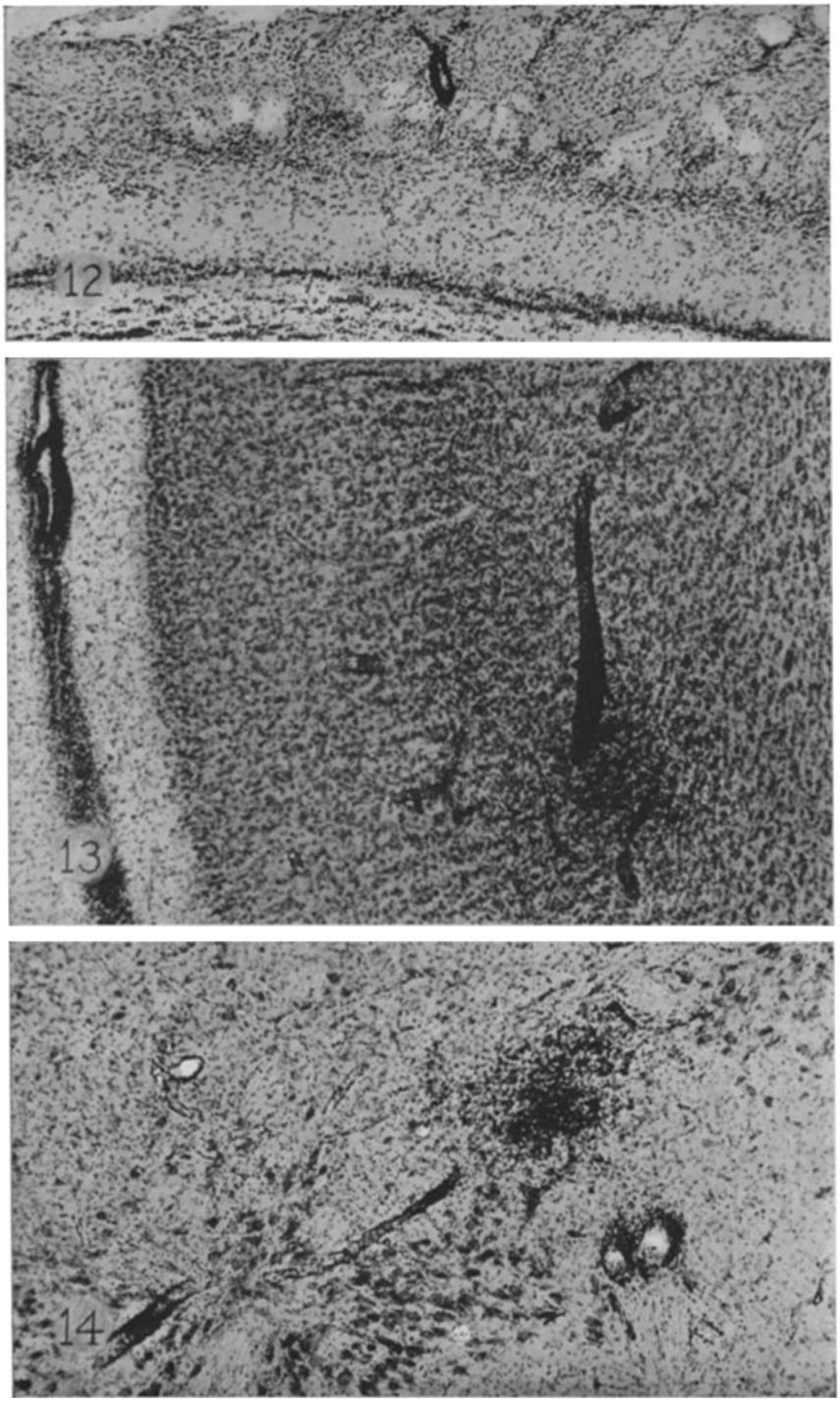
(Bodian and Howe: Non-paralytic poliomyelitis in chimpanzee)

PLATE 19

FIG. 12. Olfactory bulb of chimpanzee A4-48, with non-paralytic poliomyelitis, showing one of several perivascular and focal infiltrative lesions found, probably poliomyelitic in origin. × 60.

FIG. 13. Left postcentral gyrus of chimpanzee A4-48, showing infiltrative lesions characteristic of poliomyelitis. × 60.

FIG. 14. Substantia nigra of chimpanzee A4-48, showing infiltrative lesions characteristic of poliomyelitis. × 60.



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