NATURE OF NON-PARALYTIC AND TRANSITORY PARALYTIC POLIOMYELITIS IN RHESUS MONKEYS INOCULATED WITH HUMAN VIRUS*

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PLATES 35 TO 38

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The existence of non-paralytic or abortive poliomyelitis, although suspected, has not previously been established in monkeys either by histologic examination or by isolation of the virus on passage. In human beings the term "abortive poliomyelitis" has been applied to cases of minor illness, exhibiting usually headache, fever, vomiting, and sore throat, but not signs of involvement of the central nervous system, occurring in families or groups in which paralytic poliomyelitis was present. The isolation of poliomyelitis virus from the oral washings of two such cases by Paul and Trask (1) and the more recent demonstrations of virus in the stools of such patients (2–5) established on a firm basis what had long been suspected on clinical and epidemiological grounds. The term "non-paralytic poliomyelitis" has been used in human beings to designate cases which, in addition to the symptoms listed above, exhibit stiffness of the neck and back, pleocytosis, tremor, and other signs and symptoms of preparalytic poliomyelitis but never develop paralysis. Again the demonstration of virus in the stools of such patients in recent years (2–5) has provided proof of the true poliomyelitic nature of the non-paralytic disease. Although it is commonly stated that the central nervous system is affected in the non-paralytic but not in the abortive form of human poliomyelitis, little or nothing is known of the actual nature or extent of involvement of the central nervous system in either form of the disease.

Non-paralytic or abortive forms of experimental poliomyelitis have been recorded but rarely and then on equivocal grounds. Harmon, Shaughnessy, and Gordon (6), using fever, pleocytosis of more than 150 cells per c. mm., increase in cerebrospinal fluid globulin, neutrophilic leucocytosis in the peripheral blood, and the usual preparalytic signs (excitability or apathy, tremors, weakness, etc.) without development of paralysis

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as criteria, observed what they considered to be the abortive form in 10 out of 555 inoculations in 350 monkeys. They used monkey passage virus and the 10 animals were for the most part inoculated intracerebrally with serum-virus mixtures. No histological examination of the nervous system is recorded, but 5 of 9 monkeys tested for immunity succumbed with typical paralysis on subsequent inoculation of virus. A recent report by Kling (7) stated that *rhesus* and *cynomolgus* monkeys inoculated with human material (or drinking water) exhibited "mild paralytic" or "abortive" forms of poliomyelitis in which *no neuronal lesions* were present but only cellular infiltration of the vessels, usually those of the meninges or choroid plexus. This report did not give adequate evidence that those lesions were caused by poliomyelitis virus or any other virus, and will be discussed later on in the light of our own findings.

In the beginning of a study on the distribution and elimination of virus in human poliomyelitis it was observed that of 2 monkeys inoculated with the same specimen of stool by different methods, 1 developed typical paralytic poliomyelitis while the other exhibited only some transitory fever and questionable tremors. When the latter monkey was sacrificed 30 days after inoculation, typical poliomyelitis lesions, no longer acute in character, were discovered throughout the neuraxis. In subsequent studies 287 inoculated monkeys which failed to develop paralysis, were sacrificed at the end of 30 to 37 days and their nervous system was submitted to histological examination. The purpose of this communication is to present evidence that non-paralytic poliomyelitis occurs in monkeys inoculated with human material and to point out (*a*) that it is almost invariably associated with the destruction of an appreciable number of nerve cells in the spinal cord; (*b*) that its failure to progress to distinct paralysis depends upon an equilibrium between the virus and the host, in which the virus is not always rapidly destroyed since it can occasionally be passaged to other monkeys; and (*c*) that transitory paralysis depends upon a similar equilibrium, in which, however, it is not clear whether a certain number of cells attacked by the virus recover or whether the remaining nerve cells become sufficient for apparently normal function.

Methods

All inoculated monkeys were observed daily, or oftener if they exhibited suspicious signs of any kind. Their rectal temperature was taken daily for 30 to 35 days and they were exercised in sufficiently large enclosures to permit observation of abnormal running or climbing. Special care was taken to test for deltoid and facial paralysis. When the monkeys were sacrificed, usually 35 days after inoculation, their viscera were examined for gross pathological changes, especially for those of a tuberculous nature, and it is pertinent to state that only 2 of 400 monkeys exhibited gross evidence of tuberculosis. The entire brain and cord were examined macroscopically and six levels of the spinal cord and one of the medulla in the region of the olivary bodies were studied micro-

scopically as routine. Three lumbar, one thoracic, and two cervical levels of the spinal cord were usually obtained, care being taken to include the roots, in which the most striking evidence of previous neuronal destruction is often to be found. In addition one or two regions of the diencephalon, just caudal to the optic chiasma, were also studied in many instances, and the olfactory bulbs and frequently the anterior perforated substance were included whenever a monkey had received nasal instillations. Tissues for histological study were fixed in the Zenker-acetic mixture and as a rule stained with eosin and methylene blue. Part of the spinal cord and medulla of each monkey were stored in 50 per cent buffered glycerol at approximately 5°C., to permit passage to other monkeys whenever it was deemed necessary or desirable.

RESULTS

The diagnosis of non-paralytic poliomyelitis was made in 16 instances. Among 157 monkeys, which failed to develop paralysis following inoculation with various human tissues or with first passage virus, there were 14 with non-paralytic poliomyelitis; 11 of these were inoculated with human tissues and 3 with the nervous tissue of monkeys paralyzed by human virus. Only 1 case of non-paralytic poliomyelitis was found among 23 presumably negative monkeys which had received nasal instillations of untreated stools (8) or intraabdominal injections of etherized stool suspensions (5), or both. The remaining case of non-paralytic poliomyelitis was found in 1 of 3 monkeys which apparently failed to react when passage of virus obtained from human stools was attempted in them. Among 54 non-reacting monkeys, inoculated with nasal secretions, saliva, or urine from poliomyelitis patients, and 44 "negative" monkeys, which received various tissues of other monkeys inoculated with M.V. virus, none exhibited the lesions which warranted the diagnosis of non-paralytic poliomyelitis.

Clinical Course of Monkeys with Non-Paralytic Poliomyelitis.—The temperatures and clinical observations recorded in Chart 1 reveal a variety of responses which are so atypical that in the majority of instances it would not have been possible to predict what the histological study revealed. The temperatures were sometimes distinctly elevated for a number of days but usually were quite irregular; an occasional monkey was excited, tremulous, clumsy, or questionably weak for a few days, while many others appeared entirely normal. In the beginning many cell counts were done on the cerebrospinal fluid obtained by cisternal puncture but this procedure was abandoned later on because it could not be relied upon for diagnosis. We have even encountered as many as 500 mononuclear white cells per c. mm. of cerebrospinal fluid in a monkey, which on histological examination exhibited no poliomyelitis lesions, and whose nervous tissue upon inoculation into mice did not yield the virus of lymphocytic choriomeningitis or any other infectious agent. A comparison between the temperatures and clinical course of a number of monkeys which were histologically negative (Chart 2) with those of monkeys in which the lesions of poliomyelitis were present, reveals that on the basis of clinical observations alone it is usually not possible to make the diagnosis of non-paralytic

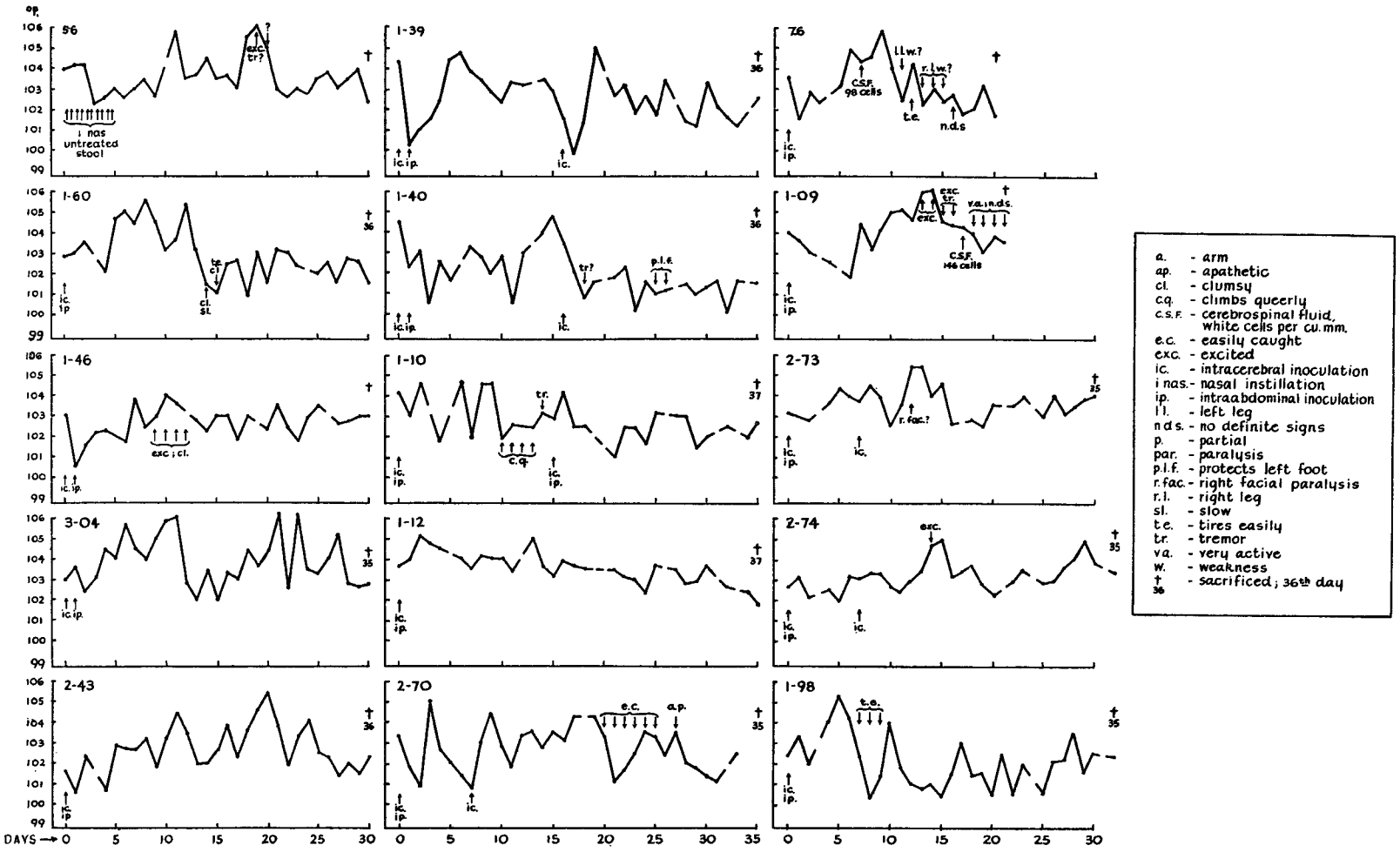

CHART 1. Temperature charts of *rhesus* monkeys with non-paralytic poliomyelitis.

poliomyelitis in monkeys. The irregular temperature curves appeared to be correlated more with activity and climatic conditions than with anything else we could discover, since these monkeys were singularly free from tuberculosis and other organic diseases with the exception of the common benign esophagostomum infections of the gut and mild parasitic infestations of the lung. When a monkey accidentally sustained a fracture

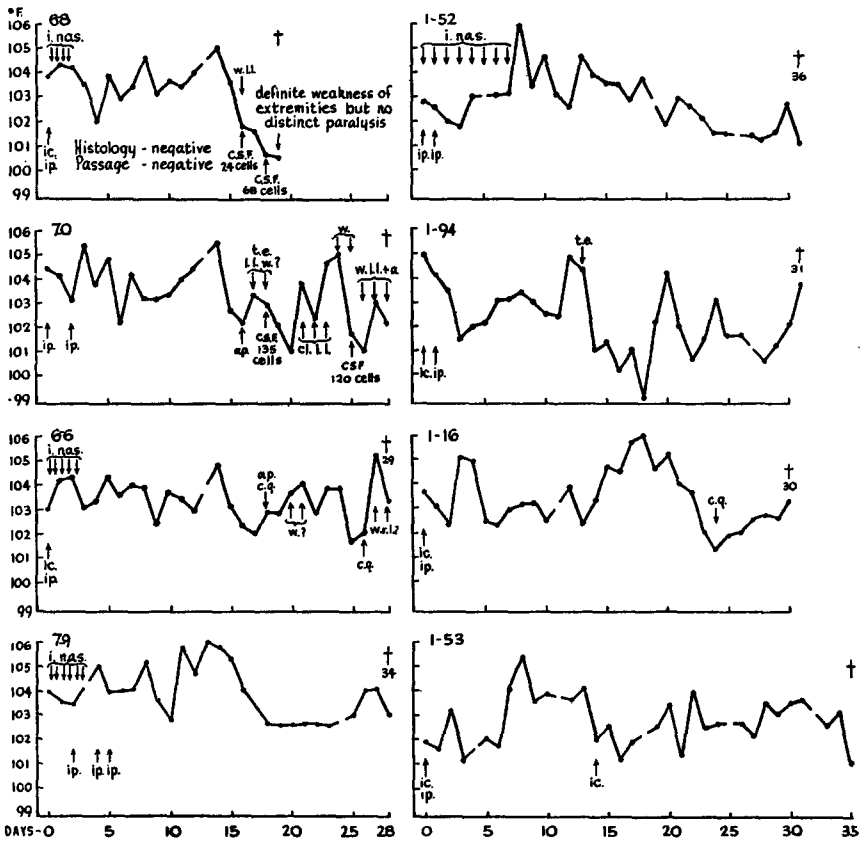

CHART 2. Monkeys with no histological evidence of poliomyelitis, but with temperatures or clinical course resembling those of non-paralytic group.

of a lower extremity or was continually kept in its cage even when its temperature was taken, remarkably flat temperature curves could be obtained.

Criteria for Pathological Diagnosis of Non-Paralytic Poliomyelitis and Results of Passage.—Monkey 5-6 (Chart 1) was the first one to be examined and the changes in its nervous system indicated the extent and character of the lesions that might be found in a non-paralytic animal. The lesions were no longer acute in character in the sense that no acidophilic necrosis of nerve cells was present, and that there were practically no polymorphonuclear leucocytes in the foci of neuronophagia or among the cells infiltrating the interstitial tissue. However this particular case was still sufficiently early to show more extensive infiltration and neuronal changes than were found in monkeys which had

apparently lived for a longer interval after the acute phase. Monkey 5-6 which had been inoculated only by the nasal route and which was sacrificed probably about 10 days after the acute phase (judging from the number of days with entirely normal temperature and physical condition) exhibited the following changes: (1) one of the olfactory bulbs was normal while the other presented marked infiltration with mononuclear cells especially in the glomerular layer; (2) there was a unilateral lesion in the anterior perforated substance with focal neuronophagia (*i.e.* glial nodules) and perivascular cuffing; (3) similar foci of neuronophagia and perivascular cuffing were also present in the hypothalamus, thalamus, mesencephalon (red nucleus), medulla, and in one anterior horn of the cervical cord; (4) the most extensive lesions, however, were present in the anterior and lateral horns of the sections of lumbar cord (Figs. 1 and 2) which exhibited marked perivascular cuffing, disappearance of an appreciable number of nerve cells in the anterior and lateral horns with considerable focal and diffuse cellular infiltration in the areas of outfall of cells, and a large number of degenerated anterior horn cells with marginated Nissl substance and eccentric nuclei. The nerve roots showed only minimal signs of degeneration at this stage.

In another instance in which the monkey (7-6, Chart 1) was sacrificed relatively early, one could find almost complete destruction of most of one anterior horn of the cervical cord (Fig. 3) with extensive interstitial infiltration and marked perivascular cuffing; an area of necrosis and neuronophagia was present in one lateral horn of the thoracic section and focal neuronophagia and perivascular cuffing in the medulla; in the lumbar sections the nerve cells appeared to be well preserved and only marked perivascular cuffing of vessels in the gray matter was present. In the few monkeys sacrificed at this early stage the reaction of degeneration in the nerve roots was still not far enough advanced to be conspicuous. In practically all the monkeys sacrificed beyond 30 days, however, wherever there was any suggestion of outfall of cells one could find reliable confirmatory evidence in the degenerative reaction which was present only in the corresponding nerve roots. Thus, in Fig. 4, one can see a section of the cervical cord of monkey 1-10 in which the nerve cells of the lateral half of one anterior horn have been destroyed with degeneration in the anterior roots of the same side, but not in those of the opposite side where all the nerve cells in the anterior horn may be seen to be intact. It is interesting to note that in the same monkey no lesions were found in another level of the cervical cord, thoracic cord, or medulla, while in three levels of the lumbar cord only two small foci of interstitial infiltration and some perivascular cuffing were present. The changes shown in Figs. 3 and 4 are especially conspicuous even at low magnification because in addition to the disappearance of nerve cells there has been destruction or distortion of the ground substance by the inflammatory reaction. In Fig. 5 is shown a cord (monkey 1-46) in which the gray ground substance of the affected anterior horn appears well preserved and there is relatively little interstitial infiltration, but that a large number of the anterior horn cells is missing is obvious not only by comparison with the anterior horn of the opposite side but also by the degenerative reaction in the anterior roots of the corresponding side. In the eosin-methylene blue-stained sections the degenerative root changes are recognized chiefly by the extensive proliferation of the neurilemmal nuclei, the numerous clear areas indicative of the loss of axis cylinders and myelin sheaths, and often by the presence of fat-laden mononuclear phagocytes. When monkeys are sacrificed during the first few days after nerve cell destruction has occurred, none of these changes are seen in the preparations of the nerve roots fixed and stained

in this manner. It is only later, when the axis cylinders and myelin sheaths of the corresponding, destroyed neurons have finally degenerated and the sheaths of Schwann and the phagocytic cells have responded, that the picture described above is most easily recognized (see Figs. 6, 7, and 8). The condition of the nerve roots is thus not only an important index to the loss of nerve cells but also to the chronicity of the lesion, indicating that the process has taken place a considerable time before the monkeys were sacrificed and that we were not dealing with animals that had very long incubation periods and would have developed paralysis if they had been allowed to live longer. When the loss of nerve cells is massive as shown in Figs. 3, 4, and 5, one does not need to be convinced of it by finding the degenerative reaction in the corresponding nerve roots. There are many instances, however, where the number of neurons affected is much smaller and one cannot be certain that there has been a loss of nerve cells without finding the degenerative reaction in the corresponding roots.

These pathological changes in the spinal cord, varying in degree and extent, were present in all the cases in which a diagnosis of non-paralytic poliomyelitis was made on histological grounds alone. These changes were sometimes limited to one level of the cord but more often they could be found at several levels, including the lumbar, thoracic, and cervical regions. In addition to the lesions in the spinal cord there were frequently perivascular cuffing and interstitial and focal glial infiltration in the substance of the medulla, hypothalamus, and thalamus. The reverse, however, was rare and a histological diagnosis of non-paralytic poliomyelitis was not considered to be warranted without evidence of neuronal lesions in the spinal cord. There was one exception to this rule, in which poliomyelitis virus was, nevertheless, isolated on passage. It is well known that in typical paralytic poliomyelitis in monkeys the virus is most readily isolated during the first few days after the onset of paralysis, and that after a period of 2 weeks the virus is only rarely found even in animals infected with monkey-adapted virus. It was, therefore, not expected that in these monkeys which were inoculated with human virus and sacrificed at a time when the lesions were already chronic, virus could be readily demonstrated by passage. Passage was, however, attempted in a number of instances because it was desirable to obtain additional proof of the true poliomyelitic nature of the lesions and also to establish whether or not virus from a monkey with non-paralytic poliomyelitis could produce the typical paralytic disease in other monkeys and thus prove that the host played a definite rôle in determining the non-paralytic nature of the infection.

The spinal cord and medulla of each of 4 non-paralytic poliomyelitis monkeys were passaged into each of 4 new monkeys with negative results. Using single monkeys, however, we have obtained irregular results even when the nervous tissue of frankly paralyzed monkeys was employed for passage. Multiple monkeys were used in sub-

sequent attempts (Table I), and positive passage was obtained in 2 instances with the development of typical paralytic poliomyelitis. It may be of interest to describe the 2 animals whose nervous tissue yielded the virus. Monkey 1-39 was sacrificed 36 days after intracerebral and intraabdominal inoculation with a pool of the lungs, liver, spleen, and kidneys from a case of human poliomyelitis. Although nothing abnormal was observed during life, the following lesions were found in the nervous system of this monkey: In the thalamic region two sections revealed multiple foci of interstitial glial

TABLE I

Passage of Nervous Tissue from Monkeys with Non-Paralytic Poliomyelitis

Tissue from Monkey No.	Passaged into Monkey No.	Result
5-6	2-76	Negative
1-12	2-78	"
1-09	2-71	"
1-46	2-69	"
3-04	3-95	"
	3-96	"
1-39	2-65	Typical paralytic poliomyelitis
	2-66	Negative
1-40	2-67	"
	2-68	"
Pool of 1-10, 1-60, 2-43	4-03	"
	4-04	"
	4-05	"
3-14	3-97	Typical paralytic poliomyelitis (subsequent passage also positive)
Atypical—lesions in medulla, none in 6 levels of spinal cord. Medulla passaged	4-06	Negative

infiltration and perivascular cuffing distributed chiefly in the tuber cinereum, thalamus, and globus pallidus. In the medulla, midcervical, and lower cervical regions of the spinal cord there were occasional foci of interstitial glial infiltration and marked perivascular cuffing. In the midthoracic level there were present in addition to these changes distinct glial nodules indicative of previous neuronophagia; in the upper lumbar, midlumbar, and sacral levels of the cord distinct outfall of neurons in the anterior and posterior horns with well-advanced degenerative changes in the roots were present in addition to interstitial infiltration and marked perivascular cuffing. It is evident, therefore, that the infection was well past its acute phase when the monkey was sacrificed; and the isolation of virus in this case indicates that while there was obviously some sort of equilibrium between the virus and the host which prevented involvement of enough cells to produce

the paralytic disease, the virus was not destroyed in the process. The other monkey (3-14) that yielded the virus was especially interesting because it did not exhibit the pathological changes which, in our opinion, were necessary for a histological diagnosis of non-paralytic poliomyelitis. It exhibited no abnormal clinical signs and was sacrificed 35 days after intracerebral inoculation of the abdominal sympathetic ganglia from a case of human poliomyelitis. Histologically, 6 levels of the spinal cord presented no sign of outfall of nerve cells, no degenerative reaction in the ventral or dorsal roots, and no interstitial infiltration or perivascular cuffing; in one section of the medulla, however, there was some glial infiltration in the reticular substance of one side and in the floor of the 4th ventricle on the other side, associated with perivascular cuffing of several vessels. 1 of 2 monkeys in which the glycerol-preserved medulla was passaged, developed typical flaccid paralysis of the extremities and the usual characteristic lesions of poliomyelitis were present in the spinal cord. Further successful passage of this virus was accomplished and it was shown to be non-pathogenic for mice.

Transitory Paralytic Poliomyelitis and the Question of Partial, Reversible Damage to Neurons.—The term "transitory paralysis," as used here, refers to a condition in which distinct though usually partial, paralysis of one or more extremities is present for half a day to about 2 days and then disappears. Although our monkeys were not always kept sufficiently long to permit detection of this condition, it has been encountered 5 times among 60 paralyzed animals. We were interested in determining, if possible, the pathological basis of the transitory paralytic disease and whether or not the rapid halt to progression as well as the regression of paralysis was associated with a disappearance of virus.

The temperatures and clinical course of 4 of these monkeys are shown in Chart 3. The first animal (8-2) is especially interesting because of the extremely short duration of paralysis, which might have been missed if the monkey's course had not suggested frequent observation. This monkey had been given 5 nasal instillations of an untreated stool suspension and one intraabdominal injection of an ether-treated suspension of the same material. When its temperature had fallen from 106.8–106.5° on the 14th and 15th days to 102.8°F. on the 16th day, it was carefully exercised in the morning but no paralysis or weakness was noted. In the afternoon of the same day (16th) there was definite partial paralysis of both lower extremities, while on the morning of the next day (17th) the monkey could climb again with no definitely discernible paralysis. It was active and well on the 18th and on the 19th day when it was sacrificed. Histologically, typical lesions were present, but the majority of nerve cells, some of which showed degenerative changes were intact, and some levels of the spinal cord appeared entirely normal. Passage of cord from this animal produced typical, prostrating, paralytic poliomyelitis in another monkey. The pathological changes in the other 3 monkeys shown in Chart 3 were more extensive in that in some regions of the spinal cord more than half of the anterior horn nerve cells had undergone necrosis and neuronophagia.

It seems clear from the histological studies on these monkeys as well as on those with non-paralytic poliomyelitis, that an appreciable number

of nerve cells must be destroyed for paralysis to become clinically apparent. When, therefore, paralysis regresses within a day or two of its appearance the question arises whether some of the nerve cells which had been damaged by the virus recover or whether the remaining cells have become sufficient for apparently normal function. It is obviously impossible to follow the fate of the same cell or group of cells under these conditions of study, but the numerous instances in which nerve cells have been found in a partially

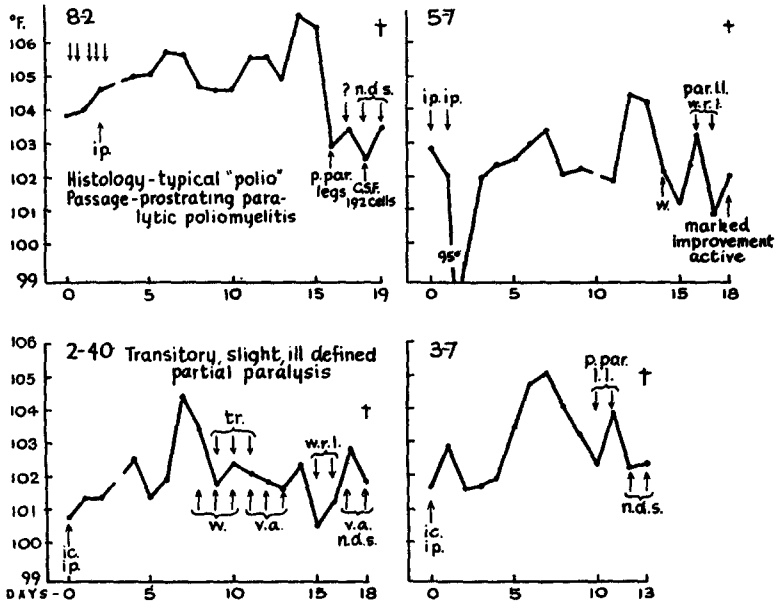

CHART 3. *Rhesus* monkeys with transitory paralytic poliomyelitis.

damaged state suggest that a cell attacked by poliomyelitis virus perhaps need not invariably be irreversibly damaged.

Fig. 9 shows part of an anterior horn from monkey 3-7 which was sacrificed 2 days after regression of paralysis. One can see in it, side by side, 1 or 2 normal cells (Fig. 11), at least 4 cells with complete chromatolysis and typical acidophilic intranuclear inclusions (Figs. 12 and 13), and several foci of neuronophagia (Fig. 14) which are no longer acute in character, *i.e.*, they are made up of glial cells rather than polymorphonuclear leucocytes (see Figs. 17 to 21 for comparison). In monkeys with non-paralytic poliomyelitis, sacrificed relatively early, one can see large numbers of cells with marginated Nissl substance and eccentric nuclei (Figs. 2, 15, and 16) side by side with other changes indicating that the process is well past the acute phase. The latter type of cytologic change has also been observed in some monkeys inoculated with human virus and sacrificed in the first few days after the onset of partial, non-progressing, though not regressing, paralysis. In monkeys with non-paralytic or transitory, paralytic poliomyelitis sacri-

ficed approximately 2 weeks or more after the acute phase, no such cells have been found; the nerve cells surrounding glial foci or areas from which cells have obviously disappeared look quite normal (Fig. 10). It would appear, therefore, that either the degenerated cells and cells with intranuclear inclusions seen during the early stages of recovery are finally completely destroyed or else that they become normal again. While it is clearly impossible to establish which of the two events occur, it is known that cells which retain their nuclei can recover and certainly cells in which the degenerative change shown in Fig. 16 has been produced by other means, *e.g.* cutting peripheral nerves, etc., can return to normal. Nerve cells attacked by poliomyelitis virus that has been thoroughly adapted to the monkey (M.V. virus) as a rule pass through the stages indicated in Figs. 17 to 21, beginning with chromatolysis and the appearance of acidophilic, intranuclear inclusions (usually seen when monkeys are sacrificed about a day before the onset of paralysis and rarely thereafter), and progressing to complete acidophilic necrosis and phagocytosis by polymorphonuclear leucocytes. The presence of cells, such as those shown in Figs. 12, 13, 15, and 16, in monkeys inoculated with human or first passage virus at a time when the host has clearly been able to check the further activity of the virus, suggests that the course of events depicted in Figs. 17 to 21 may perhaps not be completed when a certain equilibrium has been achieved between the host and the virus.

DISCUSSION

In the present study evidence has been brought forth that non-paralytic infection can occur in *rhesus* monkeys inoculated with human or first passage poliomyelitis virus. It was observed that while no reliable clinical or laboratory criteria were available, the diagnosis could be made with certainty when definite evidence of neuronal destruction in the spinal cord was found on histological examination of the nervous system. The results of this study further indicate that in the absence of such changes in the spinal cord, suspicious lesions (*e. g.*, glial aggregates) in the medulla or elsewhere in the nervous system, though rarely present without simultaneous involvement of the cord, do not warrant the diagnosis of non-paralytic poliomyelitis unless the virus can be isolated from the tissues. The agent thus isolated must, however, produce the typical paralytic disease with necrosis of nerve cells and neuronophagia in the spinal cord in other monkeys, and not merely vascular or other vague infiltrative lesions. For there is as yet no evidence that there exist strains of poliomyelitis virus without the cardinal property of producing neuronal lesions in the spinal cord and distinct flaccid paralysis. The occurrence of non-paralytic or transitory paralytic types of poliomyelitis in monkeys was found to depend upon the ability of the host to check the activity of the virus or to achieve an equilibrium with it, since it has been possible to produce the typical paralytic and prostrating type of disease by transferring tissue from these animals to other monkeys.

In a recent report, Kling (7) maintained that in monkeys inoculated with

human tissues or drinking water there occur "abortive" or "mild paralytic" attacks of poliomyelitis in which there is no evidence of neuronal damage but only cellular infiltration in the meningeal vessels and choroid plexus. On passage of the nervous tissue of such monkeys, "paresis" but not paralysis was observed, and there were again no neuronal lesions but only the vascular changes. Although no evidence was obtained that these lesions were caused by poliomyelitis virus, he suggested that he was dealing with a type of poliomyelitis virus that caused no neuronal destruction. We have observed the lesions described and illustrated by Kling in more than 50 per cent of our monkeys in which a diagnosis of poliomyelitis could not be made according to our criteria. These lesions were also present in 30 of 44 monkeys inoculated with monkey tissues in which virus was never demonstrated. We have seen a glial nodule in the medulla, perivascular cuffing, and cellular infiltration near the ventricles in uninoculated monkeys. Furthermore, several attempts to passage nervous tissue showing these vascular lesions produced no apparent disease in other monkeys, and the nervous system of these passage animals was either free of similar lesions or contained them in the same ratio found in other monkeys. We have as yet been unable to demonstrate any virus or other infectious agent pathogenic for monkeys, guinea pigs, or mice in the nervous tissues exhibiting these vascular lesions. That rabbits and mice spontaneously exhibit in their nervous system similar changes, which must be guarded against when these animals are used in experimental work, is well known, and it is our impression that the same obtains for monkeys.

The demonstration in the present study that monkeys do not need all their anterior horn nerve cells for apparently normal function, and that under certain conditions the host may achieve an equilibrium with the virus before a sufficient number of nerve cells is destroyed to produce paralysis, has a definite bearing on our interpretation of abortive and non-paralytic poliomyelitis in man. It shows, for example, that the progression of virus need not necessarily be halted before it reaches the spinal cord for the infection to be non-paralytic, as was suggested in one hypothesis (9). It is also important to note that the evidence indicates not only that the virus can reach and attack the spinal cord in a non-paralytic infection but also that it may persist for a considerable period. In this respect one cannot help but wonder whether or not certain activities or conditions may not be capable of upsetting such an equilibrium, and one recalls the frequency with which certain cases of human, paralytic poliomyelitis occur within about 24 hours of severe exertion or excessive exercise. The short interval between the exertion and the onset of paralysis suggests that the virus must

have already been present in the central nervous system at the time, and the question naturally arises whether or not an infection that might have remained non-paralytic could thus be changed into the paralytic disease by a disturbance in the equilibrium which may exist between the host and the virus.

The phenomenon of transitory paralysis which is not unknown in human poliomyelitis has in earlier days been explained on the belief that edema and inflammatory exudate temporarily interfered with the function of the nerve cells. Histological study of this condition in monkeys, however, offers no support for such a hypothesis and suggests rather that it may depend in part on the fact that apparently normal function can be carried on with less than the normal number of nerve cells, and in part on the possibility that not all nerve cells attacked by the virus are irreversibly damaged.

SUMMARY AND CONCLUSIONS

1. The occurrence of non-paralytic poliomyelitis in monkeys inoculated with human or first passage virus was proved by histological examination of the nervous system and by isolation of the virus.

2. The non-paralytic infection was almost invariably associated with the destruction of an appreciable number of nerve cells in the spinal cord, and failure of the process to progress seemed to depend upon an equilibrium between the host and the virus, in which the latter occasionally persisted in an active state since it could produce the typical paralytic disease on passage to other monkeys.

3. While there were no reliable clinical or laboratory criteria, the diagnosis of non-paralytic poliomyelitis was made when the following changes were found in the spinal cord: (*a*) outfall of neurons confirmed by the presence of the reaction of degeneration in the nerve roots, and (*b*) foci of glial infiltration and perivascular cuffing in the gray matter.

4. Anterior horn cells showing diffuse chromatolysis and acidophilic, intranuclear inclusions were present 2 days after disappearance of paralysis of short duration, and nerve cells with marginated Nissl substance and eccentric nuclei were found side by side with obviously older lesions in monkeys with non-paralytic poliomyelitis. These cytologic changes were not present in monkeys sacrificed in still later stages of the disease.

5. The transitory character of the paralysis in some monkeys may depend in part on the fact that apparently normal function can be carried on with less than the normal number of nerve cells and in part on the probable, but not proved, possibility that not all nerve cells attacked by poliomyelitis virus are irreversibly damaged.

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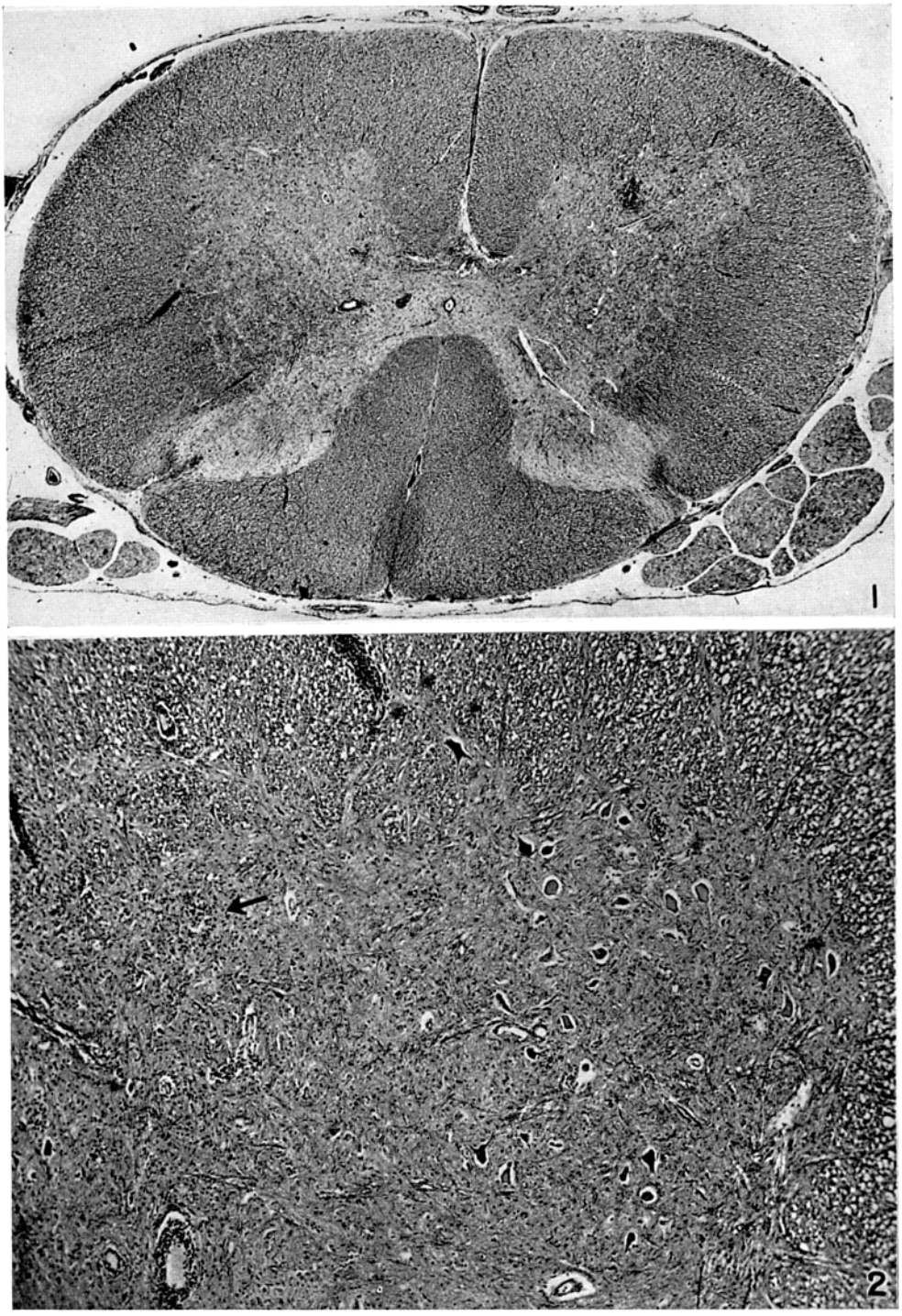
EXPLANATION OF PLATES

PLATE 35

FIG. 1. Upper lumbar cord of monkey (5-6) with non-paralytic poliomyelitis. × 19.

FIG. 2. Same; left anterior and lateral horns. Note outfall of nerve cells and cellular infiltration in lateral horn, and anterior horn cells with marginated Nissl substance and eccentric nuclei. × 65.



(Sabin and Ward: Poliomyelitis in monkeys)

PLATE 36

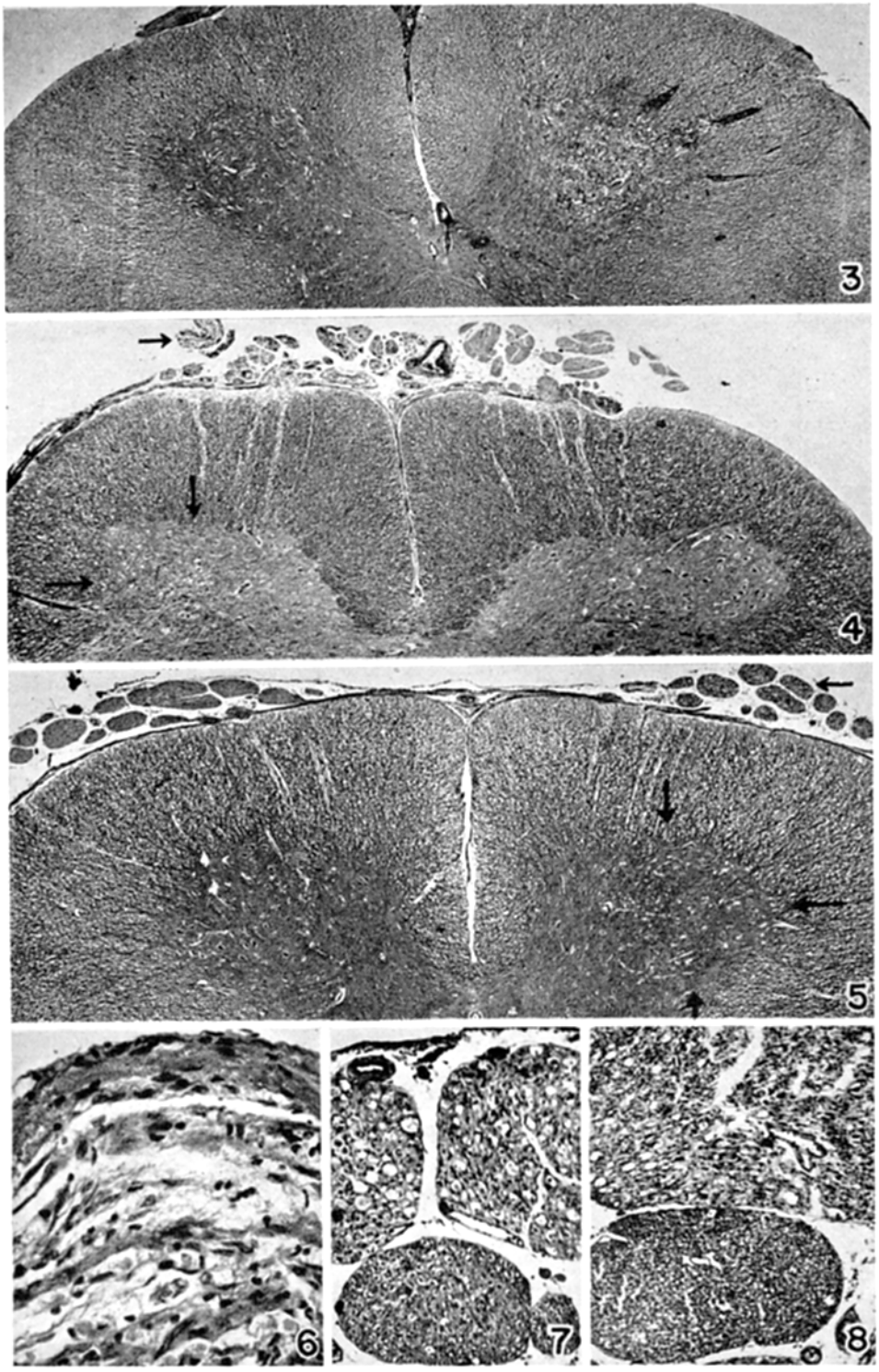
FIG. 3. Monkey (7-6) with non-paralytic poliomyelitis. Note destruction of most of the anterior horn on the right side. × 16.

FIG. 4. Monkey (1-10) with non-paralytic poliomyelitis sacrificed at later stage. Arrows point to outfall of neurons in anterior horn on the left, and to roots showing reaction of degeneration. For greater magnification see Fig. 6. × 20.

FIG. 5. Monkey (1-46) with non-paralytic poliomyelitis. Arrows point to outfall of neurons in the anterior horn on the right and to degenerated nerve roots on the same side. Note paucity of reaction in site from which neurons have disappeared. × 20.

FIG. 6. Nerve root showing reaction of degeneration. × 270.

FIGS. 7 and 8. Same. The roots in the lower portion of each figure are normal. Fig. 7, × 103. Fig. 8, × 68.



(Sabin and Ward: Poliomyelitis in monkeys)

PLATE 37

FIG. 9. Anterior horn in spinal cord of monkey (3-7) with transitory paralysis, sacrificed 2 days after disappearance of paralysis. Black arrows point to foci of neuronophagia (see Fig. 14), and white arrows to nerve cells with acidophilic, intranuclear inclusions (Figs. 12 and 13). × 68.

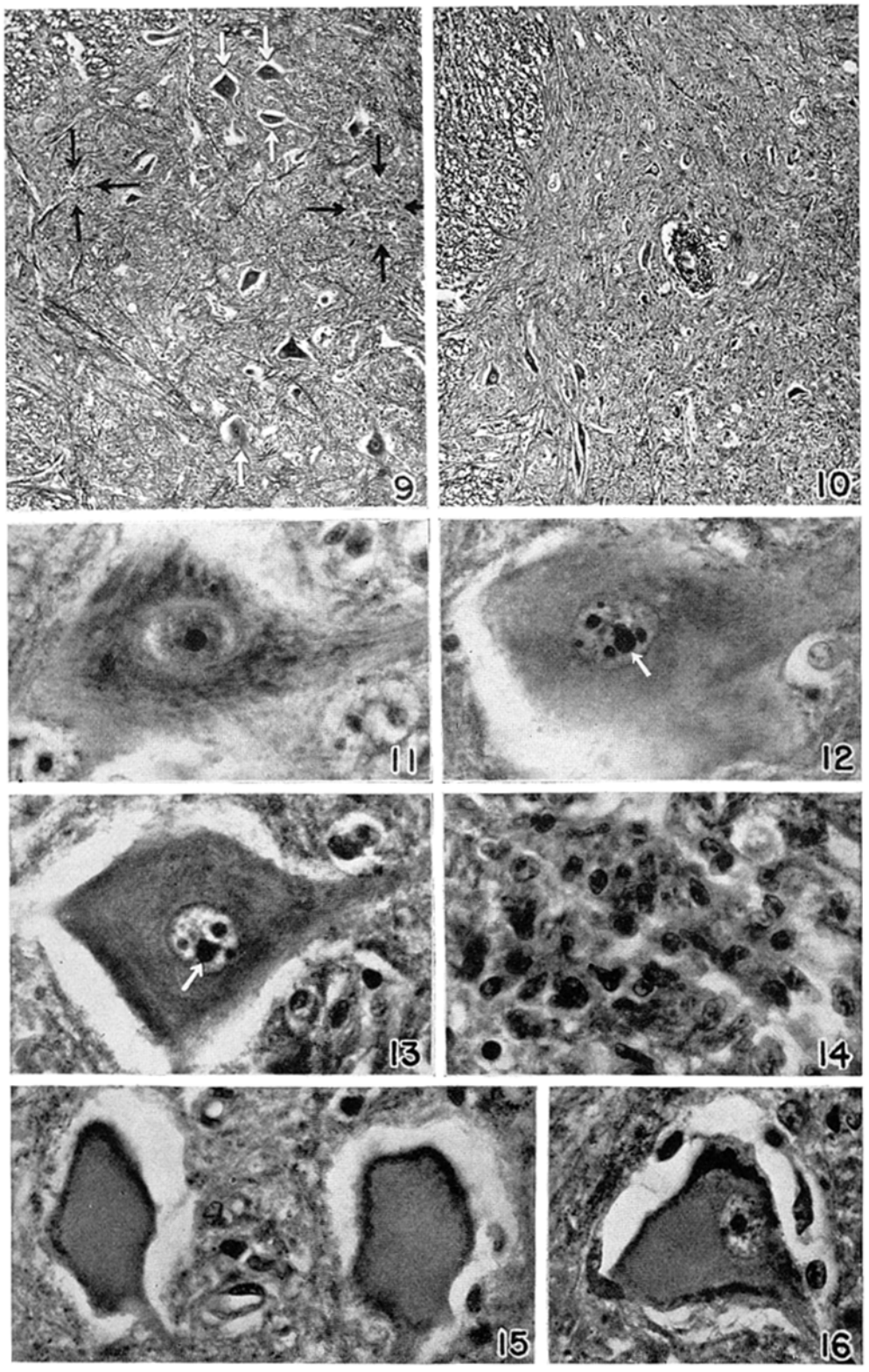
FIG. 10. Anterior horn in spinal cord of monkey (1-40) with non-paralytic poliomyelitis, sacrificed 36 days after inoculation. Note foci of cellular infiltration indicative of previous loss of nerve cells, and the normal appearance of the remaining nerve cells. × 68.

FIG. 11. Apparently normal cell from Fig. 9. × 640.

FIGS. 12 and 13. Cells showing diffuse chromatolysis and acidophilic intranuclear inclusions from Fig. 9. Arrows point to basophilic nucleoli—other intranuclear, sharply outlined, bodies are acidophilic inclusions. × 640.

FIG. 14. Focus of neuronophagia from Fig. 9. Note that it is made up chiefly of glial cells. × 640.

FIGS. 15 and 16. Anterior horn cells from Fig. 2 showing margination of Nissl substance and eccentricity of nucleus. × 640.



(Sabin and Ward: Poliomyelitis in monkeys)

PLATE 38

Figs. 17 to 21 depict the fate of an anterior horn cell attacked by monkey-adapted poliomyelitis virus. They were prepared in the course of an unpublished study on the pathology of experimental poliomyelitis produced by nasal instillation of M.V. virus, by one of us while at the Laboratories of The Rockefeller Institute for Medical Research. The photographs were taken by Mr. Joseph B. Haulenbeek.

FIG. 17. Normal anterior horn cell representative of condition of the nerve cells in the spinal cord about 3 days before the onset of paralysis. × 1000.

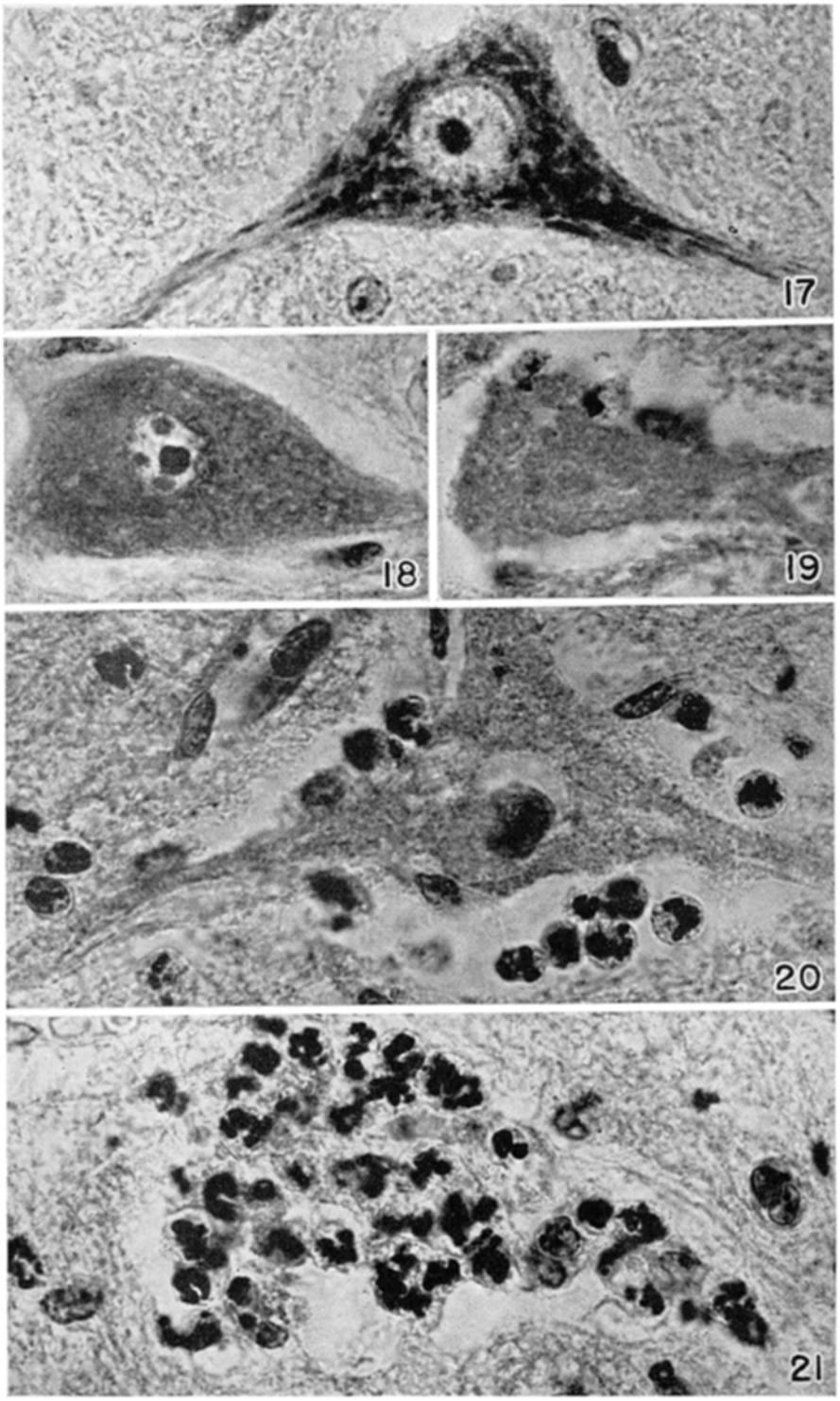
FIG. 18. Anterior horn cell showing diffuse chromatolysis and three acidophilic, intranuclear inclusions, found almost exclusively in monkeys sacrificed the day before onset of paralysis. × 1000.

FIG. 19. Complete acidophilic necrosis of anterior horn cell. × 1000.

FIG. 20. Polymorphonuclear leucocytes invading necrotic cell. × 1000.

FIG. 21. Neuronophagocytosis by polymorphonuclear leucocytes. × 1000.

The stages shown in Figs. 19 and 20 predominate on the day before paralysis while that in Fig. 21 is more prevalent during the first day of paralysis. This timing was made possible by the fact that the virus used was so well adapted that it not only regularly produced infection by the nasal route but also that paralysis appeared on or about the 7th day in almost all inoculated monkeys.



(Sabin and Ward: Poliomyelitis in monkeys)