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Experimental Poliomyelitis in a Monkey without Demonstrable Lesions in the Central Nervous System.

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Experimental poliomyelitis is quite acute in the monkey, beginning as a rule with a high fever followed in 12 to 36 hours by cerebro-spinal fluid pleocytosis of approximately 25 to 100 cells, followed then by pre-paralytic symptoms such as irritability or apathy, excitement or inertia, ruffled hair, tremors and ataxia. This stage usually lasts for several to 24 hours, after which paralysis sets in, the cerebro-spinal fluid cell count increases up to 600 or 800 cells and then paralysis becomes complete. Histo-pathological examination of the central nervous system shows as a rule extensive nerve cell destruction and cellular infiltration.

In the course of our experiments on over 700 monkeys, one animal ran an unusually protracted clinical course, both in the preparalytic and paralytic stages. More unusual, however, was the absence of any histo-pathological lesions, diagnostic of poliomyelitis. However, an emulsion of this monkey's spinal cord produced the typical dis-

* P represents a preliminary, C a complete manuscript.

ease when injected into the monkeys, intracerebrally. These unusual findings seem to be of sufficient interest to report.

The monkey had the following clinical course:

May 11—Intracerebral inoculation of a partially neutralized virus-serum combination.

May 18—Temperature 103^{8}, slight head tremor, diarrhoea.

May 20— " 104^{3}, cerebro-spinal fluid—2 cells.

May 22— " 103^{5}, cerebro-spinal fluid—11 cells; globulin trace.

May 23— " 103^{7}, cerebro-spinal fluid—28 cells; differential count—polymorphonucler cells 10%, mononuclears 90%; globulin trace.

May 24—Temperature 102^{4}, cerebro-spinal fluid—116 cells, polymorphs 15%, monocytes 83%, bilobed cells 2%.

May 26—Temperature 103^{3}.

May 29— " 104^{8}—slight weakness of legs.

May 30— " 104^{5}—Same.

June 1— " 104^{7}—Increased weakness of legs.

June 2— " 103 —Legs still weaker; cerebro-spinal fluid—5 cells.

June 3— " 99 —weakness arms; cerebro-spinal fluid—cells 5, globulin 0.

June 4—Greater weakness of the limbs, died during the afternoon.

The average normal temperature before the onset of poliomyelitis was 103^{4}F.

Histo-pathological study. Gross examination revealed a slight inflammation of the large intestine; the central nervous system showed nothing abnormal.

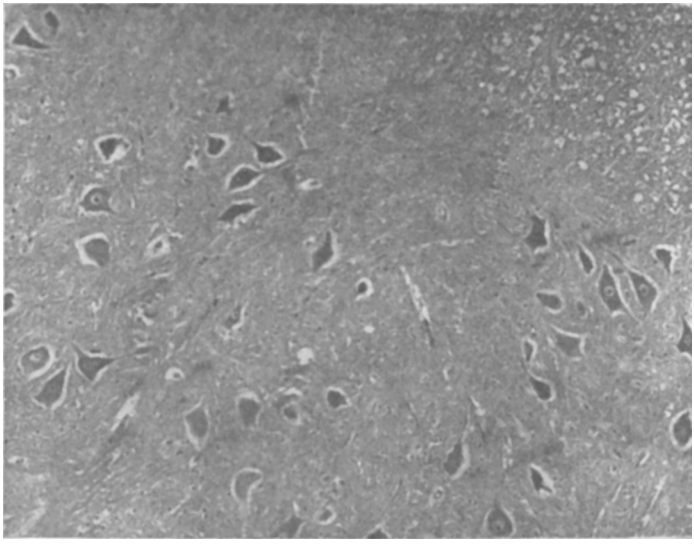

FIG. 1. Lumbar cord. Magnification 80—Phloxine—Methylene blue. No infiltration, oedema or nerve cell destruction.

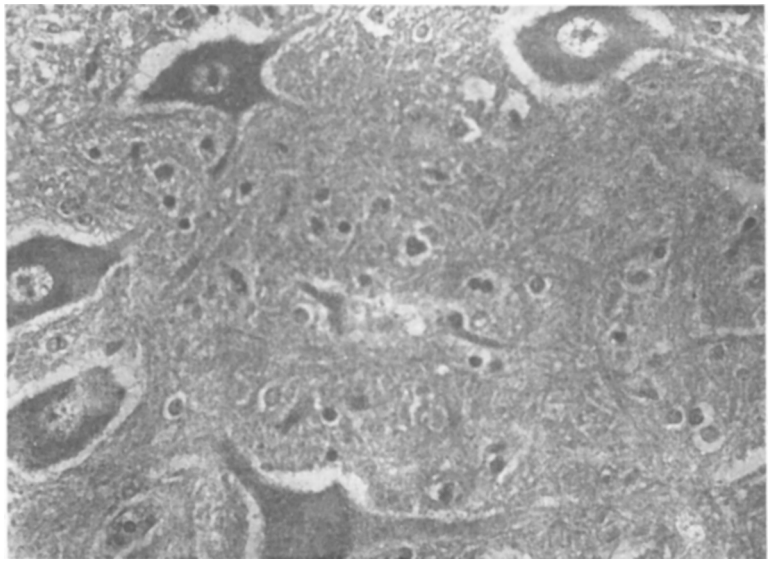

FIG. 2. Same. Magnification 360. Two small blood vessels without perivascular infiltration, no neuronophagia or satellitosis, no central chromatolysis, displacement of nuclei, edema or essential changes in any but one cell, which may be artifact.

Microscopic Examination. Examination of a number of selected blocks. The cord and brain stem were stained with hematoxylin-eosin and phloxine methylene blue. The meninges overlying the brain stem showed thickening with extravasation of red blood corpuscles, a few mononuclear cells, but elsewhere the subarachnoid spaces appeared to be entirely normal. The white matter showed no evidence of pathological changes.

The grey matter showed no hyperemia, perivascular or interstitial infiltration and no neuronophagocytosis or satellitosis. Except for the presence of a few rod cells and slight changes in some of the neurones such as central tigrolysis, shrivelling, pale or poor staining and occasional shift of the nucleus. These changes were in no way diagnostic of poliomyelitis and were found to a greater or lesser extent in monkeys that died of inter-current infection.

Although the clinical course progressed more slowly than usual, the head tremor, cerebro-spinal fluid pleocytosis and progressive weakness of the limbs were very suggestive of poliomyelitis. Moreover, the pathology outside of the central nervous system did not seem sufficient to account for the death of the animal. However, the histological findings were in no way similar to those of this condition. Nevertheless the spinal cord, when inoculated into other

monkeys gave the usual acute form of the disease with widespread nerve cell destruction and infiltration of the grey matter. On further serial passage the typical acute form was produced and the spinal cord showed the usual high infectivity. The spinal cord of the animal under discussion was infective in no greater dilution than 1:20 whereas a 1:8000 dilution of a suspension of the cords of animals running the typical acute form, gave infection.

Inasmuch as weakness developed during the last 5 days of a 10-day illness and was progressive up to the time of death, it appears that the attack of poliomyelitis was largely responsible for the death of the animal.

Of interest in this animal was the diphasic character of the attack. The first stage consisted of an increased temperature and tremors lasting 2 days, followed by a quiescent period of a week during which the animal appeared normal and then a second rise of temperature and progressive weakness. This simulates the human diphasic form described first by Medin[1] and Wickman[2] and stressed by Draper[3] (dromedary form) and although not uncommon in the experimental disease, the period of halt between the 2 phases is usually much shorter.[4] Since experimental poliomyelitis seems a disease of the central nervous system[5] exclusively the manifestations of the first stage must be due to an involvement of the upper part of the cerebro-spinal axis, possibly the thalamus, hypothalamus and midbrain; and the quiescent period due to halt of the virus in that region or its slow progress down the nerve tract until it reaches the anterior horn cells, giving the second attack. Thus, if in the experimental disease, which is entirely neurotropic, diphasic attacks occur, there is no need in the human disease to explain the first phase as due to systemic invasion, but rather to involvement of the central nervous system as Faber[6] has suggested.

Although elsewhere and in this laboratory experimental, less severe cases, with only mild grade histo-pathological changes, have been reported, in only one other instance has the virus of poliomyelitis been isolated from the spinal cord of a monkey that showed a suggestive clinical course but the absence of specific changes in the

[1] Medin, O., *Uerber eine Epidemie von spinaler Kinderlähmung Verland. d. X, Internat. Med. Kongr.*, 1890, 2.

[2] Wickman, I., *Nerv. and Ment. Dis. Monograph.* Series No. 16, 1913.

[3] Draper, G., Acute Poliomyelitis, Blakeston Son and Co., Phila., 1917.

[4] Brodie, M., and Wortis, B., *Arch. Neur. and Psychiatry*, in press.

[5] Brodie, M., and Elvidge, A. R., *Science*, 1934, **79**, 235.

[6] Faber, H. K., *Medicine*, 1933, **12**, 83.

cord. In this instance[7] the only apparent changes were vacuolization and sclerosis of the neuromes and possibly satellitosis.

These 2 cases remind me very much of Landry's[8] ascending paralysis. Therefore, I would suggest that when a case of ascending paralysis of unknown etiology and without any histo-pathological changes, as originally described by Landry and confirmed by Ormerod and Prince, Seifert, Rapper and others, or with very slight changes as described by Buzzard,[9] Williamson,[10] Stafford[11] and others, is encountered, the possibility of an unusual reaction to the virus of poliomyelitis be kept in mind and a piece of cord be removed, aseptically, for animal passage.

Conclusions. 1. A *Macacus rhesus* monkey infected with the virus of poliomyelitis ran an unusually slow course, which simulated the diphasic type found in the human. 2. The histo-pathological findings of the cerebro-spinal axis were essentially normal, but the diagnosis of poliomyelitis was made by successful passage of cord emulsion into other monkeys.

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Extraction of an Emulsion-Stabilizing Substance from Nitella with Distilled Water.

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Nitella cells, kept in distilled water for 3 days,* lose their irritability and their characteristic behavior with potassium.[1] This is apparently a result of the extraction from the cell surface of some organic substance or substances, which we may designate as *R*. Presumably *R* is constantly produced by the normal metabolism of the cell and accumulates in the cell surface if the cell is bathed by a

[7] Kling, C., Pattersson, A., and Wernstedt, W., Epidemic Infantile Paralysis, Report from the State Medical Institute of Sweden to the XV International Congress of Hygiene and Demography, Washington, 1912.

[8] Landry, *Gazette Hebdomodaire de Médecine et de Chirurgie,* 1859.

[9] Buzzard, E. F., *Brain,* 1907, **80**, 77.

[10] Williamson, R. T., Diseases of the Spinal Cord.

[11] Stafford, J. S., *Lancet,* 1915, **1**, 1172.

* This exposure to distilled water produces no sign of injury and such cells live indefinitely when transferred to pond water.

[1] Osterhout, W. J. V., and Hill, S. E., *J. Gen. Physiol.,* 1933, **17**, 87, 99, 105.