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CLINICAL, PATHOLOGICAL AND EXPERIMENTAL OBSERVATIONS ON THE "MYSTERIOUS DISEASE," A CLINICALLY ABERRANT FORM OF ACUTE POLIOMYELITIS.

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Within the last year there appeared in parts of Queensland and New South Wales, a number of cases of a mysterious disease, apparently not observed previously, which had an alarming mortality. Litchfield[1] recorded the first case from Broken Hill. The patient was a child, two years of age, which "had been taken ill suddenly and within three hours was in convulsions with a temperature of 103° F." From a blood culture a Gram-negative diplococcus was obtained, which unfortunately was not further studied. He pointed out at the time that these mysterious cases were still occurring in considerable numbers in the neighbourhood of Bourke, and that more recently the disease had affected adults as well as children. In a letter[2] I drew attention to the fact that cases with similar clinical symptoms occurred about the same time in Townsville, and that the post-mortem appearances of the brain and spinal cord of the first case were macroscopically and microscopically identical with those of a typical case of acute poliomyelitis, with extensive involvement of the grey substance of the brain. This letter was replied to by Cleland and Bradley,[3] who had examined sections of the medulla of a patient in the country case in which lesions indistinguishable from those of acute anterior poliomyelitis were present, and recorded in two other cases the occurrence of marked paresis of the limbs as an aftermath of the acute infection, and considered the possibility "that it may be due to some virus allied to that of acute anterior poliomyelitis, producing a disease which has hitherto not been differentiated from the latter."

A further contribution was made by Burnell,[4] describing an epidemic of an obscure disease at Broken Hill, with a high mortality; out of fifteen cases twelve ended fatally.

The patients suffered from great weakness, and after a period of from one to two days passed into a condition of semi-consciousness. He stated that the patient, on admission to the hospital, might be lying with both eyes open, apparently in very little pain, would on request put out his tongue, but was unable to grasp longer or complicated sentences. "A marked feature was the peculiar resistiveness, the patient gently but firmly resisting any manipulations one may attempt to make with his limbs." The temperature was elevated, ranging between 101° and 107° F. The day following the mental condition had changed, a state of profound unconsciousness had set in, with head retraction and intermittent clonic convulsions, followed later by increase in respiration, and frequently a typical respiratory death supervened. The duration of the disease in fatal cases was three to five days. In the non-fatal cases the patients never showed the respiratory embarrassment, and in two of them, after weeks of apyrexia, delusions were still present. The brain was examined in three cases, in two of them the meninges were normal, in the third there was slight injection of the *pia mater* and marked œdema of the brain substance. Otherwise the internal organs appeared normal. The cerebro-spinal fluid of seven cases out of the ten gave culturally a short, non-motile, non-spore-forming bacillus, which proved non-pathogenic to guinea-pigs and rabbits.

Cleland, Bradley and Buckley[5] in a further communication gave a short account of the mysterious disease in New South Wales. The clinical symptoms were the same as those recorded by other observers. After one or two days of malaise the patients became stuporous, semi-comatose or irritable, the temperature rose to 39.5° C. (103° F.), or even 41.7° C. (105.1° F.), and tetanic convulsions preceded death, which occurred within a week of the onset. They stated that "in the non-fatal cases there was a gradual and irregular fall of temperature and a slow improvement. In one or two cases there was paresis of the muscles of the extremities." The lumbar puncture gave a clear fluid in the majority of cases. The total mortality was 61%. The post-mortem revealed in a few cases enlarged Peyer's patches of the intestinal mucosa and enlarged mesenteric lymph glands. "Some fine punctate hæmorrhages were present in one brain, definite œdema in another, and congestion in three brains," but no obvious meningitis. The sections of the medulla and the upper spinal cord of one case (that of a child which had died at Narrabri) showed various areas of round cell infiltration, with destruction of nerve cells and congestion, a condition "very suggestive of the lesions found in acute anterior poliomyelitis." Negative results were obtained on injecting an emulsion of parts of the brain and spinal cord into the peritoneal cavity of a monkey. The authors pointed out that the cerebro-spinal fluid from other cases failed to produce any ill effect on monkeys, guinea-pigs and rabbits, and suggested the term "cerebral fever" for the condition.

Anderson[6] recorded careful clinical observations of fourteen cases of the mysterious disease from the Goondiwindi district in Southern Queensland, of which six ended fatally. Twelve of his patients were under ten years of age. The onset of the disease was sudden, with headache, high fever and convulsions, followed by deep coma. Two of his patients developed unilateral paresis, from which they completely recovered.

Mathewson[7] had under his care at the Brisbane Children's Hospital seventeen patients suffering from a similar disease, out of which number eleven died. The onset of the disease was mostly sudden. A child, previously healthy, developed a high tempera-

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ture and was seized with convulsions, which continued with intervals of semi-consciousness for days, the child afterwards lapsing into a state of stupor and finally deep unconsciousness. In other cases the onset was insidious, the child complaining of headache and vomiting, and passing afterwards into the stages of stupor and unconsciousness. Three of the six patients who recovered, had not regained normal intelligence.

The bacteriological examination of the cerebro-spinal fluid proved negative. The pathological report on the histological examination of the brain and a small portion of the upper cervical region of the cord of one case by Latham, described the main pathological changes as a "widespread congestion of the blood vessels of the brain and spinal cord and an infiltration in their adventitial sheath, with large and small mononuclear cells, including plasma cells." The ganglion cells appeared to have been but little affected, even those situated in the midst of hæmorrhages or islet of cells.

During the months of March, April and May, 1917, a number of patients were admitted to the Townsville Hospital suffering from a disease, the symptoms of which did not entirely agree with any hitherto described ailment, but corresponded in all details to the cases of the "mysterious disease" or "cerebral fever." The high mortality—out of seven cases five ended fatally—and the obscure nature of the disease warranted a careful clinical, pathological and experimental investigation.

Circumstances enabled me to obtain autopsies on five cases, and the brain and spinal cord of these cases was subjected to further histological examination. Within the last month two further cases of the same disease were observed in Townsville. Both ended fatally, and the brain and spinal cord were utilized for further investigation. The interest which the cases in question have aroused, and their obscure nature, warrant a publication of the results of the clinical and pathological observations in detail.

Case 1.—A boy, seven years of age, was admitted on March 6, 1917 (*see* Chart I.). The history showed that the boy had been "off colour" for a few days prior to admission. On March 4 he had a fit, accompanied by high fever, after which the patient became unconscious for a short time. The following day his general condition was slightly improved, and he had, to a certain extent, regained consciousness. The improvement, however, was only temporary, and his condition becoming worse, he was taken to the hospital.

On admission, the boy was semi-conscious, and looked very ill. The physical examination did not reveal any striking changes, beyond a slight stiffness of the neck and an expression of pain in his face whenever his arms or legs were moved. His tongue was furred. The Widal reaction of his blood serum was negative; the urine contained only traces of albumin, but no sediment.

In the course of the following two days his general condition remained the same, and on the third day the patient appeared slightly improved; he slept peacefully during the day, but was restless at night, throwing himself about in the bed, calling out, and repeatedly attempting to get out of bed. On the fifth day after admission his temperature had become nearly normal; he began to take interest in his surroundings and answered simple questions sensibly, but was unable to grasp the meaning of more complicated sentences, and took nourishment better. The improvement was, however, only temporary. In the course of the morning of the sixth day his temperature rose, and convulsions of short duration set in, followed by unconsciousness; in the free intervals the legs and arms showed muscular twitchings. The neck was rigid; neither Babinski's nor Kernig's sign was present, and the patellar reflexes were not exaggerated; the respiration was deep and stertorous, the rate increased to about thirty-two. On account of the inability of the patient to swallow, rectal nutrient enemata were administered.

The lumbar puncture, performed on 12th, yielded a clear cerebro-spinal fluid, apparently not under increased pressure. The sediment consisted of a small number of lymphocytes only, and proved sterile on bacteriological culture.

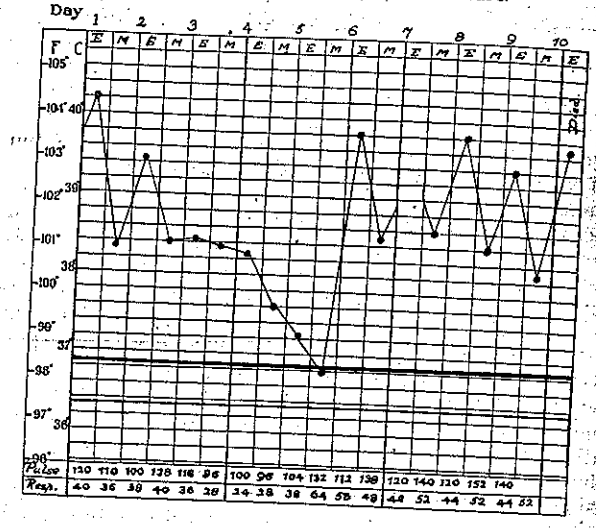

Chart I.

The patient's condition thereafter became steadily worse; he was totally unconscious, and passed his urine and small, yellow, normal motions in the bed. At frequent intervals he stiffened himself out; the fingers were partly flexed, and legs and arms shaking at first slowly, the rhythm gradually increasing, resembling somewhat a tetanic spasm. The convulsions increased steadily but slowly in frequency and severity, the respiration became more frequent and shallow, and the patient died on the tenth day after admission.

The autopsy was performed twelve hours after death. The chest organs appeared normal to the naked eye; the heart muscle was perhaps slightly flabby. There was no free fluid in the abdominal cavity, the liver showed cloudy swelling, the spleen was not enlarged, the kidneys appeared normal. The intestine was normal, the mesenteric lymph glands on the whole were enlarged and appeared on cross-section œdematous.

The *dura mater* of the brain firmly adhered to the skull. The veins of the pia-arachnoid were considerably congested. The brain substance was œdematous on cross-section, soft and congested, and the basal ganglia were the seat of numerous small hæmorrhages. On cross-section the grey substance of the spinal cord was slightly prominent, and of a pinkish grey colour, showing small hæmorrhages here and there, perhaps more numerous in the anterior horns.

Brain and spinal cord were fixed *in toto* in 10% formalin, and pieces of the different regions prepared for microscopical examination. The paraffin sections were stained with hæmatoxylin-eosin and Van Gieson's stain, by Weigert's myelin method, and with saffranin-methylene-blue-orange tannin, after having been treated with an alcoholic solution of iodine as mordant, a method utilized previously by me for staining protozoa in wet films.[8] The latter stain was

useful for the demonstration of the granules of Nissl in the ganglion cells.

Microscopically the most remarkable feature of the sections of the brain and spinal cord was the intense and general congestion of the blood vessels of the *pia mater*, and of the central nervous substance, especially of the grey matter. The perivascular lymph spaces were dilated, being here and there infiltrated with a few cells, mainly lymphocytes and a few plasma cells. Throughout the grey matter of the brain, in the cortex as well as in the large basal ganglia, were small foci of infiltration, consisting of lymphocytes and leucocytes, often but not invariably situated in the neighbourhood of ganglion cells. Similar small isolated groups of cells were noted in the white matter, but occurred less frequently, the brain tissue appearing rarefied around these foci. Many of the nerve cells were in various stages of degeneration; their outlines were irregular, their cytoplasm stained diffusely, the nucleus possessed densely staining chromatin and an indistinct nucleolus. Here and there nerve cells were surrounded by round cells, which sometimes had invaded the cells, and caused their disappearance, a process known as neuronophagia. Sometimes the neuroglia appeared slightly proliferated in the neighbourhood of these islets of cells. A number of the blood vessels showed striking changes; their walls were filled with a number of small, roundish granules of various sizes, staining dark blue with hæmatoxylin, resembling the hyaline granular degeneration of the vessel wall as found in other organs.

It was noteworthy that the lesions were irregularly distributed throughout the brain substance; hardly any foci were observed in one section, whereas numerous ones occurred in other sections of adjoining parts. Sections of the cerebellum did not reveal any lesions. The *medulla oblongata* and the spinal cord presented changes analogous to those of the brain. The blood vessels of the *pia mater* showed only a small degree of perivascular infiltration, which continued along the vessels into the spinal cord substance. The central canal appeared dilated, and the surrounding neuroglia was distinctly hypertrophic. A focal infiltration similar to that of the brain, was found irregularly distributed throughout the spinal cord, perhaps more marked in the lumbar and cervical enlargement. The whole of the grey matter showed a diffuse cellular infiltration, especially marked in the regions of the anterior horns and of the central commissure. There were numerous small islets of leucocytes and lymphocytes surrounding the nerve cells, especially the anterior polar cells; many of the cells were in various stages of degeneration, staining densely and irregularly, and not possessing Nissl's granules. In many instances only remains of the cytoplasm of the nerve cells were visible in amongst the neurophages; in other sections a clump of infiltrating cells indicated the position from which the nerve cell had disappeared. One can thus easily trace all stages of neuronophagia from the earliest stages, where the leucocytes and lymphocytes—here called neurophages—begin to surround the nerve cells, to the latest stage, where the nerve cell had completely disappeared.

The histological examination of several of the spinal ganglia showed somewhat similar lesions. A well marked, diffuse infiltration was noticed here and there, and a distinct degeneration of a few of the nerve cells.

Case 2.—A boy, nineteen years of age, a painter by trade, was admitted on April 1, 1917. The history revealed that he had not been feeling well for nearly a week, and had had a severe fit on the day prior to entering the hospital, succeeded by unconsciousness. The patient was totally unconscious on admission; his arms and legs were trembling; his head was turned to one side and his neck stiff. His facial expression denoted great pain on the attempt to turn his head. His eyes were usually fixed, showing now and again slight nystagmus; the breathing was shallow, and slightly increased in frequency. Whenever touched, the patient became quite stiff, his hands were slightly bent in the wrist joint, the thumb straight and the fingers slightly flexed. His temperature was elevated (*see* Chart II.). The patient never

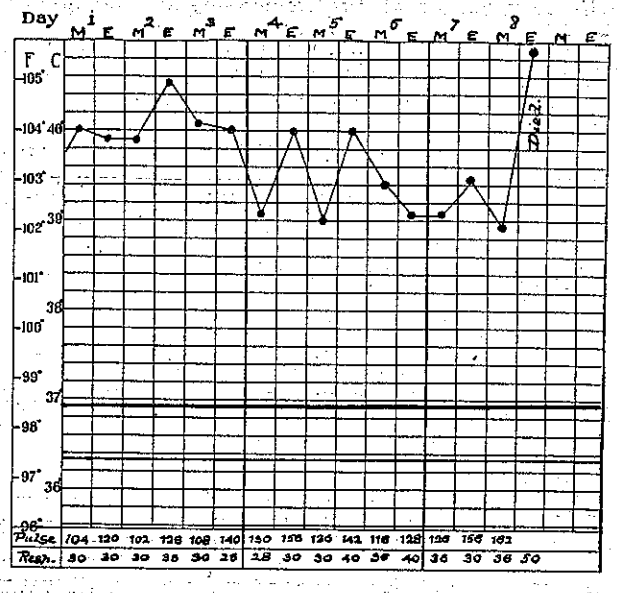

Chart II.

regained consciousness; he sank into a deeper and deeper stupor, emaciating visibly from day to day, and finally died on the eighth day. Kernig's and Babinski's sign were absent. Lumbar puncture was performed on the second and sixth day; the spinal fluid was clear, apparently not under increased pressure, dripping out slowly drop by drop from the needle. The sediment showed a marked increase in formed elements; the sediment consisted of lymphocytes, leucocytes and a few red blood corpuscles. No micro-organisms could be detected on microscopic examination, and the cultivation on the usual culture media, and, besides, on trypsin agar and on human blood serum, gave entirely negative results.

The autopsy was performed six hours after death. The pericardium contained about 5 c.cm. of clear, straw-coloured fluid. The heart was flabby, and its muscle friable. In the left pleural cavity, between the base of the lung and diaphragm, a small amount of thick, whitish fluid was found. Otherwise, the lungs and pleura were normal. The liver showed cloudy swelling, the gall-bladder was filled with dark, greenish bile. The spleen was not enlarged; the kidneys and intestine showed no changes.

The *dura mater* was firmly adherent to the skull. The pia and arachnoid were hyperæmic, the pial veins distended and filled with clotted blood; the convex surface of the brain was covered with a very thin layer of greyish exudate. The congestion was more pronounced over the occipital part of the brain, where

the veins could be easily traced to their finest capillary branches. The meninges of the spinal cord showed similar changes. On cross-section the brain substance was soft and œdematous, and its blood vessels distended. Throughout the grey matter there were numerous hæmorrhages. Larger hæmorrhages could be detected in the medulla, especially marked below the ependym of the ventricle. The ventricle system of the brain and the central canal of the spinal cord were distended and filled with clear fluid. The spinal cord on the whole did not appear much altered to the naked eye; its substance was œdematous and hyperæmic, and there were a few hæmorrhages in the grey matter of the commissure of the lumbar swelling.

Sections were prepared of the various parts of the brain and spinal cord and examined microscopically.

The microscopical examination of the meninges of the brain showed a very marked cellular infiltration, consisting of leucocytes and lymphocytes, a pronounced distension of the blood vessels and small hæmorrhages here and there. This cellular infiltration continued along the vessels into the cortex of the brain. Sections through the large basal ganglia of the brain showed a slight but diffuse infiltration of the grey substance with round cells and a dilatation of the blood vessels. The perivascular lymph spaces were dilated and filled with coagulated lymph containing a few red blood corpuscles. There were numerous small hæmorrhages destroying the brain tissue, the blood corpuscles being in various stages of disintegration. The wall of the blood vessels showed here and there striking changes, whereby the intima and media were not well defined and the vessel wall was filled with irregular small granules of varying sizes, staining dark blue with hæmatoxylin. The majority of the ganglion cells appeared normal.

The meninges of the spinal cord showed a change similar to that of the brain, a marked cellular infiltration, consisting mostly of leucocytes, which continued along the vessels into the surface layer of the spinal cord; the vessels were distended, and small hæmorrhages were not rare. The grey substance showed a slight but well marked cell infiltration, which was irregularly distributed, more pronounced in sections through the lumbar swelling, affecting mostly the tissue surrounding the central canal.

Although sixteen pieces of the spinal cord at different levels were microscopically examined, only one section, and that through the upper part of the cervical enlargement, showed neuronophagia. One of the ganglion cells of the anterior horn was surrounded by a number of mononuclear cells, forming thus a typical focus. The nerve cells on the whole appeared normal. Sections through the spinal ganglia showed normal conditions.

In the liver tissue there was microscopically a small amount of hæmorrhagic infiltration between the acini. The kidney, spleen and lymph glands did not show any noteworthy changes.

Case 3.—A boy, one year and eight months old, was admitted to the hospital on April 26, 1917. His mother stated that the child had been in perfect health until mid-day, when he suddenly had a fit and became unconscious. Six hours afterwards he was taken to the hospital in an unconscious condition, with a subnormal temperature and a pulse-rate of 140. The muscles of his legs, arms and face were twitching continuously; his head was turned to the side. The neck was not stiff; both pupils were slightly dilated and equal, and he showed neither squint nor nystagmus. The following day his temperature rose to 40.5° C. (*compare* Chart III.) and his pulse-rate was 170; cold packing for one hour reduced the temperature to 38.9° C. His bowels acted at first frequently; the stools were loose, greenish-yellow and slimy. In the course of the next few days there was hardly any change in his general condition. The patient was unconscious, twitching at intervals. On the eighth day the respiration-rate, which had been nearly normal up to then, increased in frequency; the breathing became more and more distressed, and the child died on the tenth day after admission of respiratory failure.

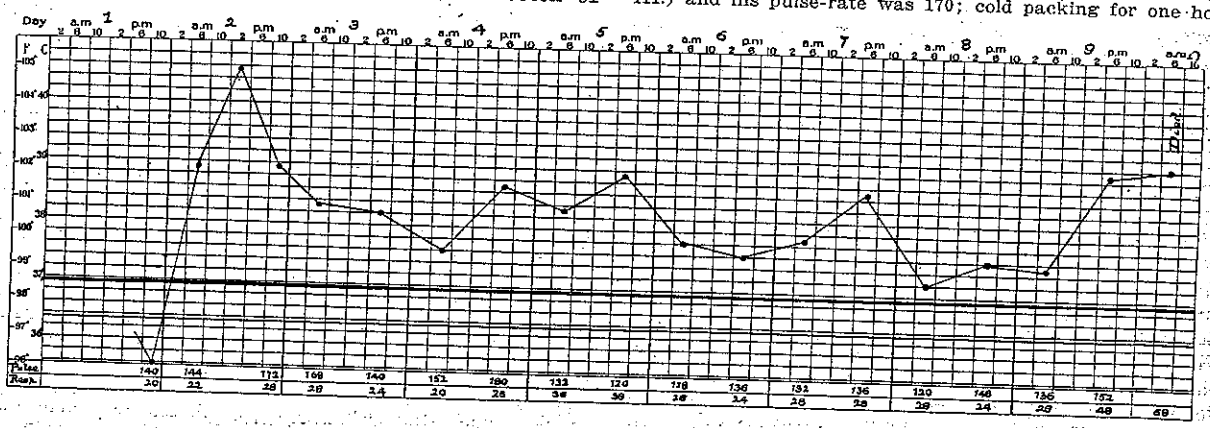

Chart III.

Lumbar puncture was performed on two occasions. The cerebro-spinal fluid was clear, and apparently not under increased pressure. The sediment contained a small number of leucocytes and lymphocytes and neither microscopical nor cultural examination revealed the presence of micro-organisms.

A post-mortem was performed two hours after death. The chest organs were normal. The liver was slightly enlarged, and in an advanced stage of fatty infiltration. All the other abdominal organs were macroscopically of normal appearance.

The *dura mater* of the brain was firmly adherent to the skull. The meninges were hyperæmic, the veins greatly distended and filled with dark fluid blood. The brain substance on cross-section was œdematous, soft and hyperæmic, but hæmorrhages could be discovered neither in the grey nor in the white matter. The ventricular system was slightly distended. The

meninges of the spinal cord were of similar appearance to those of the brain. The spinal cord substance was œdematous and congested.

The microscopical examination of sections through the cortex of the brain showed no cellular infiltration of the meninges. The brain substance revealed slight cellular infiltration, which was most marked in sections of the large basal ganglia. The vessels were congested, the perivascular spaces distended. In sections of the *thalamus opticus* a few of the ganglion cells were surrounded by a number of mononuclear cells. The cerebellum appeared microscopically normal.

Sections through the pons, medulla and spinal cord showed a few foci of cellular infiltration, most marked in the neighbourhood of the dilated central canal and in the grey substance of the anterior horns. A few small hæmorrhages were seen in the grey matter of the spinal cord, especially in that of the lumbar swelling.

The microscopical examination of the liver revealed a diffuse, fatty infiltration of the liver cells, which often completely obscured its structure, and numerous small hæmorrhages were observed.

Sections of the kidney, spleen, intestine, heart muscle and spinal ganglia did not show any pathological lesions.

Case 4.—A girl, thirteen years of age, was admitted to the hospital on May 21, 1917, in the afternoon. Her employer stated that the girl had been "feeling slightly off colour" on the previous day, but still had a good appetite. During the morning of the day of admission she felt decidedly ill, and complained of headache; about mid-day she suddenly had a fit, with workings of the leg, arm and face muscles, and she became unconscious. She arrived at the hospital about 5 p.m. in an unconscious state. Her temperature was 40.5° C., her pulse-rate 132; the pulse was regular and of good quality. The respirations were deep. The patellar reflexes were exaggerated, but ankle clonus was absent. Babinski's sign was present in both feet, but Kernig's sign was absent.

Shortly after admission the patient passed a loose, dark brownish, offensive stool. The urine did not contain albumin or sugar.

A lumbar puncture was performed the following morning. The spinal fluid was clear, not under increased pressure, and the sediment contained a small number of leucocytes and lymphocytes. Cultures of the sediment on ordinary media, on trypsin agar and human blood serum remained sterile. The patient did not regain consciousness; the temperature rose to 41° C., and she died the following day at noon.

The autopsy was performed one hour after death. The thoracic organs were normal, with the exception of two small foci of infiltration at the back of the lower right lobe of the lung. The liver was slightly enlarged, showing on cross-section traces of fatty infiltration.

The *dura mater* adhered firmly to the skull. The meninges of the brain and spinal cord were hyperæmic. The brain substance appeared on cross-section soft and œdematous and congested. In the grey substance, especially in that of the *thalamus opticus* and *nucleus caudatus*, numerous small hæmorrhages were seen. The grey matter of the spinal cord appeared prominent on cross-section, of pinkish grey colour, with numerous small, punctiform hæmorrhages.

The brain and spinal cord were fixed in formalin, and sections prepared for microscopical examination.

The meninges of the brain showed microscopically a slight but diffuse infiltration with round cells, which was more marked around the blood vessels, and continued along the vessels into the surface layer of the brain. The cortex was diffusely infiltrated with leucocytes and small round cells, which formed here and there small foci, the neighbouring brain substance appearing rarefied. Small, irregular hæmorrhages were scattered throughout the cortex and white substance. The large basal ganglia showed lesions of a similar nature, but more pronounced. There was a marked small cell infiltration in the adventitial sheath of the larger and medium-sized blood vessels; the cells were composed of lymphocytes, polymorphonuclear leucocytes and plasma cells, interspersed with larger cells possessing a large vacuolated nucleus, poor in chromatin. Below the ependym of the ventricles, as well as generally distributed throughout the grey matter, one could notice roundish or irregular foci, where the brain substance appeared rarefied, and was represented by an open meshwork of glia, with small collections of leucocytes and lymphocytes in the meshes. Smaller and larger, irregular hæmorrhages were commonly observed, and in several sections a few of the larger vessels were surrounded by a mantle of free red blood corpuscles.

A number of the ganglion cells were surrounded by cells—neurophages—and many of the nerve cells appeared in various stages of degeneration.

Sections through the pons and medulla showed analogous changes. A well marked small cell infiltration was observed around the medium-sized and larger blood vessels, and the same roundish areas of softened tissue, invaded by leucocytes and lymphocytes, were of frequent occurrence in the grey matter. The cerebellum seemed to have escaped entirely, and, excepting for congestion, the sections showed normal conditions.

In sections through the spinal cord similar lesions to those of the brain were seen, irregularly distributed, but to a greater or lesser extent present in every section. The inner layer of the pia-arachnoid was infiltrated, which infiltration followed along the vessels into the surface layers of the spinal cord. The most striking feature was numerous irregular hæmorrhages in the grey substance, mostly situated in the central commissure and in the posterior horns. Similar hæmorrhages were also present in the adjoining white matter, and a number of the ganglion cells of the anterior horn were surrounded by red blood corpuscles.

A diffuse round cell infiltration was well marked throughout the grey matter, the infiltrating cells often forming small foci. Many of the ganglion cells showed profound changes, their nuclei often staining diffusely, and their nucleoli had disappeared; neuronophagia was only occasionally seen.

A number of spinal ganglia were examined microscopically; some of the nerve cells stained diffusely, their nuclei having disappeared, otherwise no marked changes were observed.

Sections of the portions of the lung which appeared infiltrated, showed the typical picture of capillary pneumonia.

Sections of the heart, spleen, kidney, mesenteric and inguinal lymph glands appeared normal. Sections through the liver showed cloudy swelling, fatty infiltration and small hæmorrhages.

(To be Continued.)