

# *Acta Medica Okayama*

---

*Volume* 10, *Issue* 4

1956

*Article* 1

SEPTEMBER 1956

---

## Pathology of “landry-guillain-barré syndrome” in children, prevailing in the regions surrounding the Inland Sea of Japan

Takuzo Oda\*

Seiji Akagi†

\*Okayama University,

†Okayama University,

# Pathology of “landry-guillain-barré syndrome” in children, prevailing in the regions surrounding the Inland Sea of Japan\*

Takuzo Oda and Seiji Akagi

## Abstract

Histopathological investigations were carried out on five fatal cases of a type of polyneuritis of unknown etiology diagnosed as Landry-Guillain-Barre syndrome, which endemically occurred in children in the regions surrounding the Inland Sea of Japan. The most characteristic pathologic feature in the nervous system was pronounced patchy degenerative changes with slight or moderate degree of inflammatory cell response of focal type in the peripheral and cranial nerves, predominantly in the nerve fibers of the spinal and cranial roots. In the spinal cord, medulla, pons, and in some portions of the cerebrum and cerebellum, engorgement of the small blood vessels as well as edema and the less predominant scattered degenerative changes of ganglioncells and nerve fibers with extremely slight degree of glial response and sparse perivascular cell collections were encountered. The cerebrospinal meninges displayed edema and congestion of the pial blood vessels with focal collections of a small number of lymphocytes and/or monocytes. No advanced involvement of the anterior horn of the spinal cord in a strict sense of anterior poliomyelitis was, however, recognized. These changes may lead the histopathologic diagnosis of the present disease to infectious encephalomyelo-polyradiculoneuritis or a type of infectious polyneuritis. The main histopathologic changes in the visceral organs were a moderate degree of engorgement of the small blood vessels, degeneration of parenchymatous organs such as the liver and kidney, hyperplasia or follicular atrophy of the lymphatic tissues, interalveolar pneumonia, focal myositis, and slight degree of round cell infiltrations in the interstitial tissues of the other viscera, such as the liver, heart, and gastrointestinal canal. Based upon the observations on the histopathological changes as well as clinical manifestations, discussions were made on the pathogenesis and etiologic factor of the present endemic disease with critique on the literatures.

---

\*Copyright ©OKAYAMA UNIVERSITY MEDICAL SCHOOL

Acta Med. Okayama 10, 4, 175—213 (1956)

**PATHOLOGY OF "LANDRY-GUILLAIN-BARRÉ SYNDROME" IN CHILDREN, PREVAILING IN THE REGIONS SURROUNDING THE INLAND SEA OF JAPAN**

By

Takuzo ODA and Seiji AKAGI

*Department of Pathology, Okayama University Medical School*

*(Director : Prof. S. Seno)*

*Received for publication May 24, 1956.*

Since the end of 1949 many cases of a type of polyneuritis of unknown etiology have occurred in children in the regions surrounding the Inland Sea of Japan including Okayama district as the endemic center. The main clinical manifestations of the disease consisted of widespread flaccid paralysis with loss of tendon reflexes mostly beginning in the lower limbs and extending upwards, involvement of some of the cranial nerves, and paresthesia with intense radiculalgia. The cerebrospinal fluid showed in most cases slight or moderate increase in the protein content without a concomitant increase in the number of cells (albumino-cytologic dissociation). Excepting some fatal cases, all cases showed complete recovery from the paralysis with no residual atrophy from a few months to one year after the onset of the disease. According to the clinical observations, it was diagnosed as Guillain-Barré syndrome or Landry-Guillain-Barré syndrome in the children clinic of our school (Director : Prof. E. HAMAMOTO). The total number of the patients examined in the clinic from 1949 to 1955 was 125. Of those, 19 serious cases died showing the symptom of Landry's paralysis. Autopsy was carried out on five cases, four from our clinic and one from the Okayama National Hospital.

Since the initial description of a type of polyradiculoneuritis associated with albumino-cytologic dissociation by GUILLAIN, BARRÉ and STROHL (1916)<sup>16)</sup>, a large number of similar cases have been reported by many investigators in the world including Japan<sup>14), (22), (23), (25), (31), (43), (44), (45), (59), (61)</sup> under a great variety of names, such as Guillain-Barré syndrome, infectious polyneuritis or polyradiculoneuritis, primary infectious polyneuritis, infectious neu-

ronitis and others. So far as we know, however, there is no report treating an endemic outbreak of such a great number of cases in a short time and in a restricted area as the present. The etiologic factor of the present disease has not yet been established and the pathogenesis has likewise remained uncertain, in spite of the profound clinical and epidemiological observations on this disease<sup>18),19)</sup>.

The present study is based upon an investigation of the five fatal cases of the Landry-Guillain-Barré syndrome (of 2, 4, 10, 13 and 15 days' durations, respectively), and offers observations on the morbid anatomy of the disease, aiming at the clarification of the characteristics of its histopathologic changes and of the pathogenesis of the morbid process, by which the etiologic factor of the present endemic disease might be suggested.

### Report of Cases

#### Clinical Findings and Main Autopsy Diagnosis in Each Case

Case 1. — A. S., a four year old girl, was admitted to the Pediatrics of our school on Jan. 29, 1951, complaining of flaccid paralysis of all extremities. Since 10 days before the admission, she had mild diarrhea three to five times a day, which subsided one day prior to the admission. Seven days prior to the admission she had temporary slight fever of a few hours' duration. Since 2 days before the admission coughs continued without fever. On the morning of her admission, she awoke with flaccid paralysis of four extremities, which was more marked distally, and she was unable to either stand or crawl. Her speech became slow and her voice became weak. There was poor respiratory control, and force of coughs was diminished, which made her unable to bring up sputum sufficiently. She complained of severe itching in her nasal cavities and ohrs and on the soles of her feet, and of muscular pain in her legs, which made her cry when her mother moved her body. Examination revealed flaccid paralysis of all extremities and absence of all tendon reflexes, such as biceps, triceps, patellar, and Achilles tendon reflexes on both sides, and of some of superficial reflexes, such as abdominal wall and cremaster reflexes. No pathologic

reflex was elicited. Hypesthesia was not clear, for she was too young. Consciousness was intact. When she cried, the left corner of her mouth was not retracted upward, making her face asymmetric, which indicated facial paresis of the left side. No ocular disturbance was present. Slight stiffness of the neck was present and positive Kernig's sign was elicited. Deglutition reflex was very weak. Both her pulse count and body temperature were normal. Dermographismus was positive in slight degree. Hyperhydrosis was marked. Auscultation revealed stertor over the whole parts of the lung, but the percussion of the lungs did not reveal any dullness. The spinal fluid examined on the day of onset of the disease was clear and colorless; the initial pressure 200 mm. of water and the final pressure after taken 5 c.c. of the fluid 180 mm. of water; cell count 5 per cubic millimeter, of those lymphocytes 4 and neutrophils 1; Pandy's test positive; protein content measured 146 mg. per 100 c.c.; sugar content normal. The blood picture: hemoglobin 9 g/dl, R B C 4,470,000, W B C 5200; neutrophils 48%, eosinophiles 2.4%, basophiles 0%, lymphocytes 42.4%, monocytes 4%, plasma cells 3.2%. Course: on the second day severe muscular pain in legs and itching in the nasal cavities, and flaccid paralysis in all extremities persisted. Pain by pressure was felt along the sciatic nerves. She complained also of hot sensation on both legs, and hyperhydrosis was found on the whole body. Kernig's sign and nuchal rigidity increased in intensity. In the afternoon the respiration became accelerated, considerably superficial and laborious. Towards evening, the respiration became dyspneic and the pulse became tachycardic and then bradycardic. Ten minutes after the respiration stopped, the heart ceased beating and she died at 7 p. m., Jan. 30, 1951.

*Clinical Diagnosis:* Guillain-Barré Syndrome

*Main Autopsy Diagnosis:* 1. Encephalomyelopolyneuritis, characterized with degenerative changes. 2. Inter-alveolar pneumonia and catarrhalic pneumonia. 3. Parenchymatous degeneration of the heart, liver and kidneys. 4. Moderate degree of engorgement of the small blood vessels and mild edema in various organs. 5. Follicular atrophy of the spleen and lymph-nodes. 6. Atrophy of the adrenal cortex.

Case 2—H. O., a 4 year and 10 month old girl, was admitted to the Pediatrics on July 1, 1952, complaining of flaccid paralysis of all extremities. Since one week before the admission, she had mild upper respiratory symptom with cough and hyperhydrosis but without fever. Two days prior to the admission she complained of pain in her legs, and while she was taking a bath weakness of her legs developed, which was more marked distally, and she fell down twice. The next morning she awoke with marked weakness of both legs and she was unable to stand up. In the afternoon of the same day, weakness developed in her upper extremities too, and her voice became gradually low. Pain in the legs became more severe, causing bad humor, and her sleep was disturbed. She had absolutely no appetite and neither stool nor urination took place since. On the third day of the disease, when she was admitted, examination revealed flaccid paralysis of the lower extremities and flaccid paresis of the upper extremities; patellar and Achilles tendon reflexes were absent on both sides. Biceps and triceps reflexes were diminished, but she was able to hold up her upper extremities. Abdominal wall reflex remained. No pathologic reflexes were elicited. No hypesthesia was recognizable, while she complained of severe spontaneous pain in her lower legs. Mild nuchal rigidity and Kernig's and Lasègue's signs were present. There were neither facial paralysis nor ocular disturbances at that time, and deglutition reflex was normal. Consciousness was clear. Dermographismus was positive. There were a few spotty haemorrhages of small finger-tip size on her chest. The tonsils were hyperemic and swollen. Auscultation revealed small or middle sized vesicular râle over the inferior bulk of the left lung and systolic murmur over the apex of the heart. The pulse was somewhat accelerated and counted 140. There was mild edema in the lower legs. Examination of urine disclosed no abnormality, except mild positive sugar reaction. The blood picture: hemoglobin 80 %, R B C 4,540,000, W B C 10,600; neutrophils 72.4 %, eosinophiles 0.8 %, basophiles 0 %, lymphocytes 25.6 % and monocytes 1.2 %. The spinal fluid examined on the fourth day of the disease was almost clear but slightly tinted red; the initial pressure 120 mm. of water and the final pressure after taken 5 c.c. of the fluid zero; lymphocyte

count 10 and red cell count 500 per cubic millimeter; Pandy's test positive, Nonne's test slight positive; protein content measured 62 mg. per 100 c.c. Course: On the fourth day she complained of severe spontaneous pain on her four extremities and on her abdominal wall and hot sensation on her body. In the morning she was unable to hold up her arms because of complete flaccid paralysis of the upper extremities. Force of cough was diminished. The respiration became accelerated, considerably superficial and laborious. Cyanosis appeared on her lips. At noon the diaphragm was paralyzed on the right side, and the respiration became dyspneic. Towards evening facial paralysis on the right side appeared. Pulses became more frequent and the Cheyne-Stokes' respiration appeared and she died at nine p. m., July 2, 1952.

*Clinical Diagnosis:* Landry-Guillain-Barré Syndrome

*Main Autopsy Diagnosis:* 1. Polyradiculoneuritis. 2. Mild degeneration of ganglion-cells in the spinal cord, and formation of small necrotic foci in the hypothalamic nucleus. 3. Mild edema in the central nervous system. 4. A polelike clotted blood in the subarachnoidal space. 5. Pinpointed hemorrhages in the left posterior horns of the spinal cord. 6. Engorgement of small blood vessels in the leptomeniges, brains, spinal cord, lungs, kidneys, liver, digestive canal, and various endocrine organs. 7. Spotty hemorrhages in the upper lobe of the left lung, adrenals, and spleen. 8. Bronchitis, peribronchitis, interalveolar pneumonia, and catarrhalic pneumonia in the lower lobes on both sides. 9. Mild interstitial inflammation in the heart, liver, salivary glands, pancreas and skeletal muscles. 10. Mild enteritis. 11. Moderate fatty degeneration of the liver. 12. Cloudy swelling of the kidney. 13. Hyperplasia of lymph-nodes. 14. Atrophy of Langerhans' islands of the pancreas.

Case 3—N. M., a 8 year and 7 month old boy, was admitted to the Pediatrics on the third day of the disease, complaining of flaccid paralysis of all extremities and disturbance of speech. About seven days prior to the onset of the disease his family caught cold and he himself felt mild general malaise. His temperature went up to 39.9°C accompanying no respiratory symp-

tom. The temperature soon went down to the normal, and he had no abnormality since. Six days later, while he was playing baseball game, weakness of his both legs and diplopia developed and he was unable to keep standing well. Towards evening he noticed disturbances of his speech and difficulties in taking off his clothes. The next morning he awoke with flaccid paralysis of all extremities associated with severe pain in his neck, shoulders, waist and all extremities. Disturbances of both chewing and swallowing developed, showing the presence of trigeminal and bulbar paresis. On the third day of the disease, when he was admitted, examination revealed paresis of some of the cranial nerves, such as the oculomotorius, facialis, hypoglossus, and flaccid paresis of some of the upper extremities and complete flaccid paralysis of the lower extremities; biceps and triceps reflexes were diminished, patellar and Achilles tendon reflexes were absent on both sides. Deglutition reflex was diminished. Sensibility was normal except the presence of pain on the body. The sciatic nerves were painful on pressure. Mild nuchal rigidity and Kernig's sign were present. Consciousness was clear. Dermographismus was positive. Auscultation revealed dry rhonchi over the inferior bulk of both lungs. Examination of urine and feces disclosed no abnormalities. The blood picture: hemoglobin 90 %, R B C 4,250,000, W B C 11,150; neutrophils 67.6 %, eosinophils 1.2 %, basophils 0 %, lymphocytes 28.8 %, and monocytes 2.4 %. The spinal fluid examined on the day of admission was clear and colorless; the initial pressure 270 mm. of water and the final pressure after taken 15 c.c. of the fluid 80 mm.; cell count 5 per cubic millimeter, all of those lymphocytes; globulin reaction was negative; protein content measured 31 mg. per 100 c.c. Course: The next day, the fourth day of the disease, movement of both his upper and lower extremities became possible, predominantly in the right side, and facial paresis slightly recovered, while pain on her waist and extremities became severe. There were mild or moderate paralysis of some of the cranial nerves; mild in the 3rd, 4th, 6th, 7th and 11th, and moderate in the 5th, 10th and 12th. On the sixth day, though pain and itching persisted, he became to move his neck and to speak and sing well. Sputum gradually increased in quantity. Since the eighth day paralysis of the

extremities and disturbances of speech developed again, and respiration and heart action became accelerated. On the ninth day pulse became irregular and on the tenth day, Jan. 8, 1951, he died.

*Clinical Diagnosis: Guillain-Barré Syndrome*

*Main Autopsy Diagnosis:* 1. Acute encephalomyelopolyneuritis. 2. Catarrhalic pneumonia with severe engorgement of alveolar blood vessels. 3. Subacute lymphadenitis of simple type in the mesenteric lymph-nodes. 4. Engorgement of small blood vessels in the terminal part of the ileum, colon ascendens, spleen, kidney, and various lymph-nodes. 5. Periportal accumulation of lymphocytes in the liver. 6. Mild parenchymatous degeneration of the kidney.

Case 4—H. K., a 2 year and 5 month old infant, was admitted to the Pediatrics on the third day of the disease, complaining of flaccid paralysis of four extremities. About one month prior to admission, he complained of itchy sensation on his abdominal and waist skin, which continued several days. Since a few days before the onset of paralysis respiratory symptoms associated with cough had developed and one day prior to the onset his temperature went up to 39.8°C, which soon went down to the normal. The next morning he awoke with pain in his waist and hips and with weakness of the right leg, which was more marked distally. Towards evening movement of his hands became impossible. On the morning of the second day of the disease his lower extremities paralyzed flaccidly on both sides and paresis of the upper extremities developed continuously. Speaking and ocular movement were disturbed. Marked hyperhydrosis was present. Hyperesthesia and paresthesia were present in the lower extremities. On the third day, when he was admitted, respiration and heart action were slightly accelerated. Tonsils were hyperemic and swollen. Conjunctivae were slightly hyperemic, and serious fluid ran out of his nasal cavities. Deglutition reflex and cremaster reflex were present, but abdominal wall reflex was absent. Biceps and triceps were normal, while patellar and Achilles tendon reflexes were lost on both sides. Kernig's and Lasègue's signs were present. No pathologic reflexes were elicited. Examination of urine and

feces showed nothing particular. The blood picture : hemoglobin 102%, R B C 4,720,000 W B C 14,600 ; neutrophils 38.4%, eosinophiles 6.4%, bazophiles 0.8%, lymphocytes 48.8%, and monocytes 5.6%. The spinal fluid examined on the day of admission was clear and colorless ; the initial pressure 340 mm. of water and the final pressure after taken 15 c.c. of the fluid 280 mm. of water ; cell count 4 per cubic millimeter, all of those lymphocytes ; Pandy's test positive ; protein content measured 31 mg. per 100 cc. Course : On the furth day pain increased in intensity in the shoulder, upper extremities and waist. Incontinencia urinae appeared. On the fifth day his temperature went up to 37.8°C. On the sixth day dispnea and nuchal rigidity appeared. On the eighth day movement of eyes was disturbed, and paralysis of the right trigeminus developed. On the eleventh day radiologic examination revealed bronchopneumonia in the right lower lobe. On the thirteenth day, Sept. 27, 1951, dyspnea became more severe and he died.

*Clinical Diagnosis* : Guillain-Barré Syndrome

*Main Autopsy Diagnosis* : 1. Moderate acute polyneuritis. 2. Mild aute myelencephalomyelitis. 3. Hemorrhagic pneumonia. 4. Bronchitis purulenta. 5. Congestion of the spleen. 6. Parenchymatous degeneration of the liver and kidney. 7. Hemorrhage in the adrenals. 8. Atrophy of the thyroid glands.

Case 5 — E. Y., a 7 year and 4 month old girl, was admitted to the Pediatrics of the Okayama National Hospital on the eighth day of disease, complaining of flaccid paralysis and severe pain in the four extremities. Ten days prior to the onset of disease, she seemed to catch cold and complained headach. Her temperature went up to 38.7°C, but in the next morning it went down to the normal, and she had no abnormality since. Nine days later, while she was walking along a mountain path on her school excursion, weakness developed in her legs and she fell down on the ground eight times. Since the night of that day she complained severe pain in her lower extremities. The next morning, when she awoke, she was unable to stand because of flaccid paralysis of lower extremities. The paralysis and pain ascended upwards till it extended to the upper extremities. During six days she was unable to move any extremi-

ty. Since two days before admission, her upper extremities began to move slightly but her fingers remained absolutely paralysed and she could not grasp anything. The spontaneous pain became severer, which disturbed her sleep. No stool took place since onset of the disease. On the eighth day, when she was admitted, examination revealed absence of patellar and Achilles tendon reflexes on both sides. Biceps was normal and triceps was slightly diminished on both sides. All the pyramidal signs were free. Nuchal rigidity and Kernig's and Lasègue's signs were present in high degree. There was no disturbance in the cranial nerves, and she could masticate and swallow anything normally. Along the course of the sciatic nerves every points were tender on pressure. Hyperesthesia was present everywhere. The blood picture: hemoglobin 65%, R B C 4,040,000, W B C 20,400; neutrophils 82%, eosinophiles 3%, lymphocytes 12%, and monocytes 3%. The spinal fluid examined on the eighth day of the disease was clear and colorless; the initial pressure 120 mm. of water and the final pressure 80 mm. after taken 10 c.c. of the fluid: cell count 74 per cubic millimeter, most of those lymphocytes; Pandy test moderately positive and Nonne-Apelt's test positive; protein content measured 155 mg per 100 c.c. Course: the pain persisted obstinately. Since the twelfth day her respiration became dyspneic, and closing power of the lips and eye-lids became insufficient, which indicated the appearance of facial paresis. X-ray picture of the chest taken on the fourteenth day showed dark shadow in the right lung, which revealed the development of pneumonia, but her body temperature remained normal. On the fifteenth day, Oct. 10, 1950, she died.

*Clinical Diagnosis:* Infectious Myeloradiculoneuritis

- Main Autopsy Diagnosis:*
1. Moderate acute polyneuritis.
  2. Engorgement of small blood vessels and edema in the central nervous system.
  3. Mild degeneration of ganglion-cells and slight proliferation of glia cells in the pons, cerebellum, medulla and spinal cord.
  4. Inter-alveolar pneumonia and bronchopneumonia.
  5. Parenchymatous degeneration of the liver and kidney.
  6. Engorgement of small blood vessels in various visceral organs.
  7. Mild hyperplasia of lymph-nodes.

## Histopathologic Observations in Various Organs

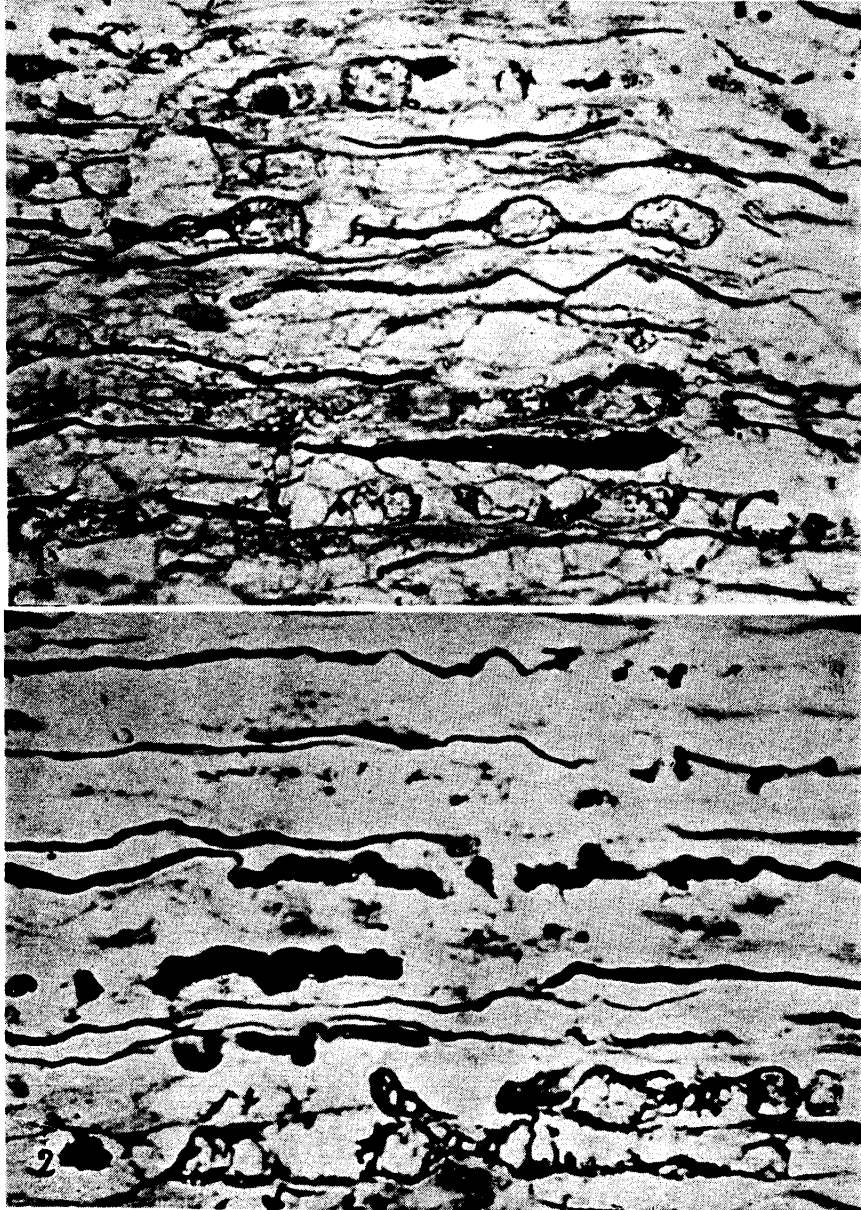
### A. Nervous System

*Necropsy findings, gross.* The brain, spinal cord and peripheral nerves disclosed in all cases slight or moderate degree of swelling, by an increase in the bulk of both the white and the grey matters, and congestion of the pial blood vessels. The weight of the brains generally increased. In Case 2, a polelike clotted blood was found in the left back part of the subarachnoidal space extending from the level with the 8th thoracic segment to the end of the spinal cord. On sectioning the brains and spinal cord, small foci of congested blood vessels were observed in all cases and clusters of pinpointed hemorrhages were recognized in some parts of the cerebral cortex in Case 1 and of the left posterior horns of the spinal cord in Case 2. On the whole, however, the macroscopic changes were neither so severe nor characteristic.

*Microscopic observations.* Sections taken from the brains, spinal cord, cauda equina, cranial nerves, spinal roots, dorsal root ganglia and peripheral nerves were stained by hematoxylin-eosin for general purpose, toluidin blue method for NISSL granule stain, BODIAN's silver impregnation method and BIELSCHOWSKY's method for nerve fibers, WEIGERT's, KULSCHITSKY's and MARCHY's method for myelin sheath, and MASSON's trichrome stain for various elements ; in some instances CAJAR's method for glia fiber, Sudan III stain and HONDA's method for degenerated myelin sheath were employed.

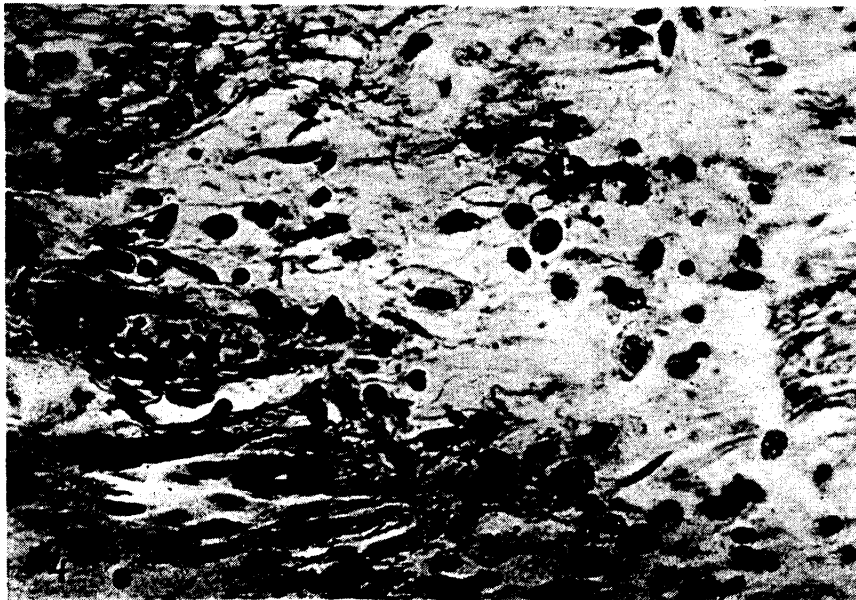
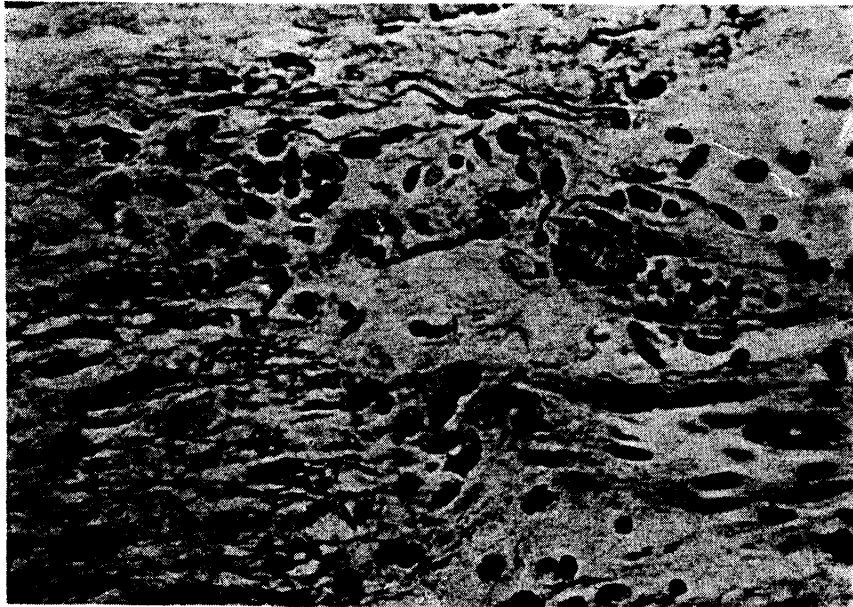
1. *Spinal roots, dorsal root ganglia and peripheral nerves.* The most profound changes were encountered in the peripheral nervous system, predominantly in the nerve fibers of the spinal roots. The most striking changes were found in preparations stained by the BODIAN's method, in which the nerve fibers of the spinal roots exhibited in all cases a marked degree of swelling. The earliest changes were indicated by edema, swelling of the myelin sheaths and enlargement of the axis cylinders. These were presented even in Case 1 in which the patient had died 2 days after the onset of symptoms. At the 4-day stage (Case 2), more advanced lesions were indicated by the irregular, ragged outlines and distortion of some of the swollen axis cylinders

(Fig. 2) and by the rosary formation with numerous beadlike varicosities or vacuolations (Figs. 1 and 2). In some areas the



Figs. 1. and 2. Pronounced degenerative changes of the nerve fibers of the 5th and the 7th thoracal roots in Case 2. Note the irregular outline and formation of numerous varicosities in some of the swollen axons in figs. 1 and 2, and corkscrewlike distortion and fragmentation and/or dissolution of some of the swollen axons in fig. 2. BODIAN silver impregnation; Fig. 1.  $\times 414$ , Fig. 2.  $\times 593$ .

nerve fibers were dissoluted and considerably reduced in number; those which remained displayed various stages of degenera-



Figs. 3 and 4. Radiculoneuritis in the 5th thoracal roots in Case-2. Note the degenerative and disintegrative changes of the myelin sheaths accompanying with inflammatory cell response, such as macrophages and lymphocytes. MASSON trichrome stain ; Fig. 3.  $\times 421$ , Fig. 4.  $\times 412$

tion, such as fragmentation or corkscrewlike distortion (Fig. 2), and resulting in a moderate degree of disintegration of some of nerve fibers accompanied with cell collections (Figs. 3 and 4). The myelin sheaths also showed various stages of degeneration, characterized by poor or absent impregnation; i. e. diffuse, irregular swelling and breaking up into droplets, some of which are scattered along the degenerated axis cylinders (Figs. 5 and 8). The myelin droplets gave the reaction of neutral fat, which was

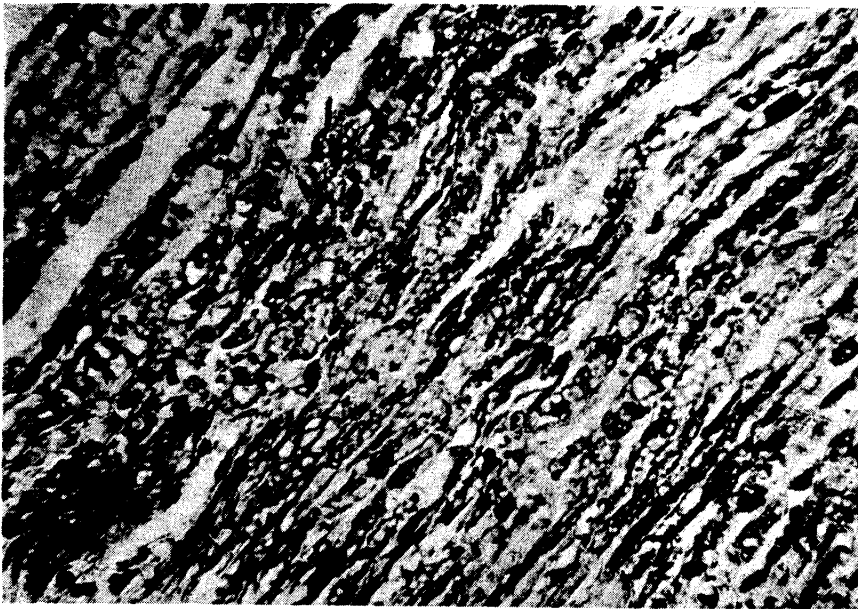


Fig. 5. Degenerative changes of the nerve fibers of the 7th thoracal roots in Case 2. MASSON trichrome stain;  $\times 250$

presented even at the 4-day stage (Case 2) moderately and after 10-day stage (Case 3) markedly with the Sudan III staining or by the HONDA's method. Cellular reaction or inflammatory exudate was apparently observed even in the early stages, such as the 4-day (Figs. 3 and 4) and the 10 day stages. Small or moderate number of macrophages and lymphocytes were encountered among or along some of the degenerated nerve fibers and around the perineural dilatated blood vessels. In some areas occasionally appeared a few neutrophils (in Cases 2, 3 and 4) and even eosinophiles (in Case 4), in which the inflammatory changes were most predominant. All the changes mentioned above varied in degree in each case of different duration and in

different parts of the peripheral nervous system. As a whole, they were usually most prominent in both the moter and sensory roots from the point of their penetration of the spinal meninges to the region where both the roots join to form the spinal nerve. The degree of changes diminished in the distal parts of periphe-  
 ral nerves, although in some portions of peripheral nerves, e. g. sciatic nerves, very slight (in Cases 1 and 2) or moderate (in Cases 3, 4 and 5) degree of degeneration of the nerve fibers or disintegrated foci with celllural response were observed. Moreover the changes were not universal in a root or peripheral nerves, but usually varied in severity from nerve to nerve in the same case, from fascicle to fascicle in the same nerve trunk and even from fiber to fiber in the same fascicle (Figs. 1, 2 and 18). For instance, in Case 2 the changes were most severe in the spinal roots of the 4th and 5th cervical segments, the 5th and 7th thoracal segments, the sacral segments and the cauda equina. In the dorsal root ganglia<sup>7),57)</sup> there was mild swelling or chromatolysis of some of the nerve cells, accompanied with or with-

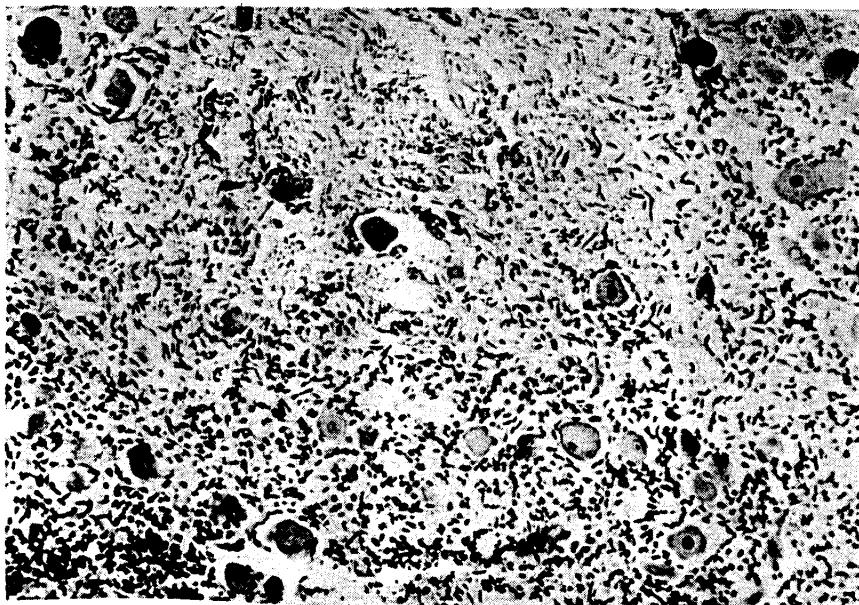


Fig. 6. The 8th thoracal dorsal root ganglion in Case 2. Mild swelling or degeneration of some of the nerve cells and proliferation of capsule cells with collection of a few lymphocytes. Ethanol fixation, Hematoxylin-eosin stain ;  $\times 143$

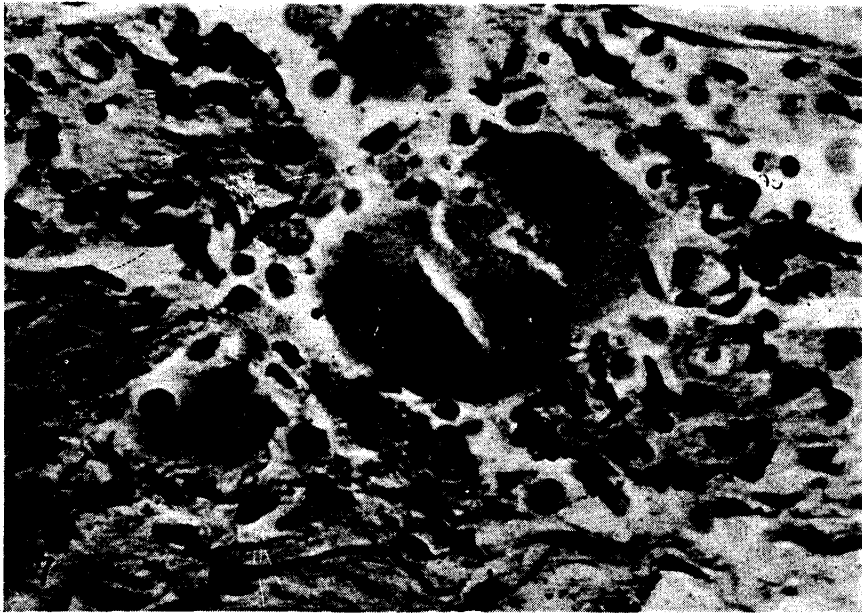


Fig. 7. The 1st. sacral root ganglion in Case 2. Degeneration of a nerve cell and dilatation of blood capillaries as well as small bleeding and collections of a few monocytes and lymphocytes around the nerve cell. Ethanol fixation, Hematoxylin-eosin stain;  $\times 678$

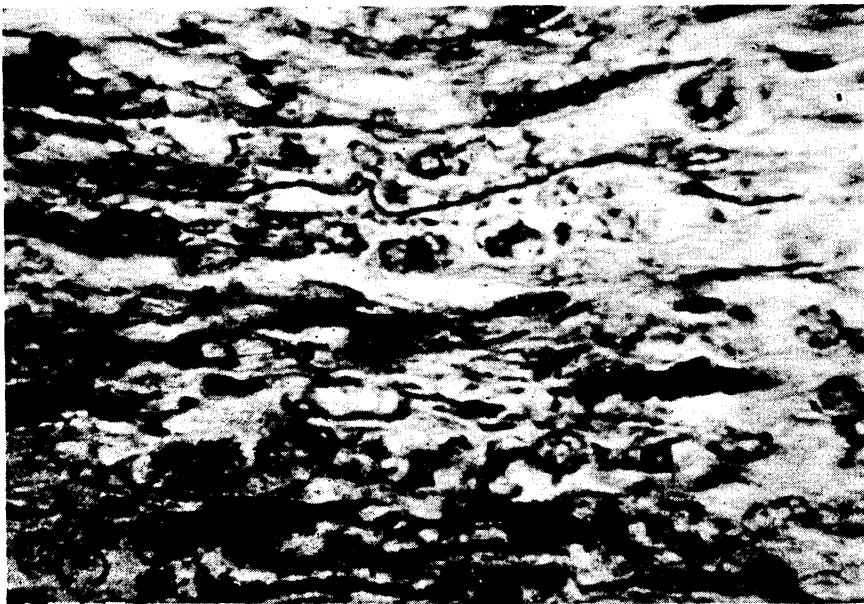


Fig. 8. Degeneration of myelin sheaths of the nerve fibers of the cauda equina in Case 2. WEIGERT stain;  $\times 400$

out proliferation of the endocapsular cells and in rare instances collection of small number of lymphocytes (Figs. 6 and 7). The changes were mild in Case 2, of 4-days' duration, and marked in Case 5, of 15-days' duration. The changes in the cauda equina were similar to those of spinal roots (Figs. 8 and 9).

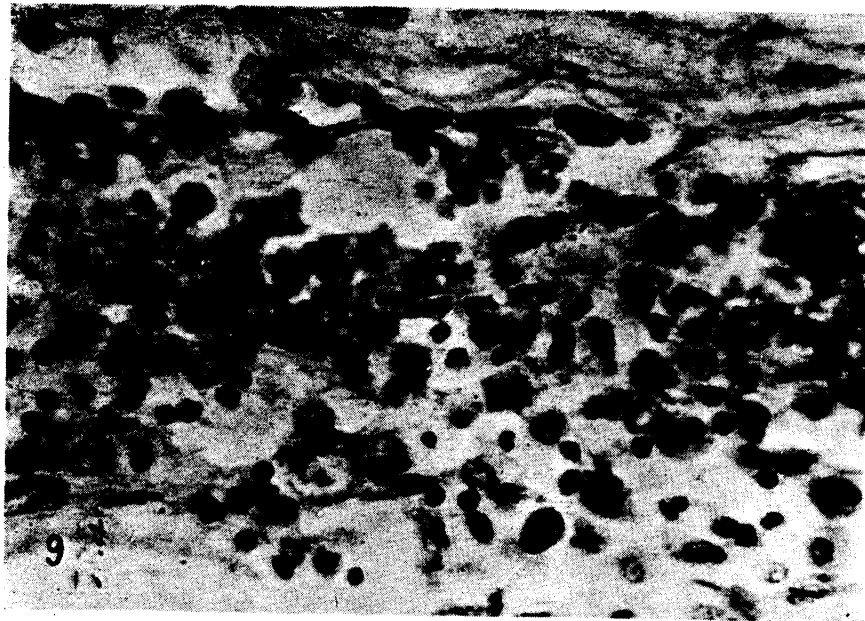


Fig. 9. Engorgement of veins and perivascular infiltrations of moderate number of monocytes as well as lymphocytes and a few neutrophils in the nerve fibers of the cauda equina in Case 2. Hematoxylin-eosin stain;  $\times 684$

2. *Spinal cord.* Sections taken from various levels of the spinal cord and stained with hematoxylin and eosin failed, as a rule, to reveal any abnormalities other than edema and engorgement of blood vessels in all cases and small bleeding in only one instance (Case 2). Preparations stained with toluidine blue revealed slight or moderate degree of alterations of some of the anterior as well as posterior horn cells such as acute swelling and chromatolysis, predominantly of central nature (Fig. 10 and 11). These changes were not universal but varied in severity from segment to segment in the same case and from cell to cell in the same horn (Fig. 11); in Case 2 the changes were relatively apparent in the 4th and 5th segments of the cervical cord and in the 5th and 7th segments of the thoracic cord, while in Case 3 in the lumbar cord. The nerve fibers within both the anterior and the posterior horns showed edema and slight degree of



Figs. 10 and 11. Degeneration of nerve cells of the anterior horn of the lumbar cord in Case 3. (Degenerative and inflammatory changes in the spinal roots and peripheral nerves were well advanced in this case). Note acute swelling or chromatolysis of some of the nerve cells. Remains are almost normal, and there is no glial response. In fig. 11, there are one nerve cell which shows acute swelling (a flatfish cell) (right) and one almost normal nerve cell (left). NISSL stain; Fig. 10,  $\times 107$ , Fig. 11,  $\times 536$

degeneration; the changes in axis cylinder were presented with the BODIAN's silver impregnation method and those in myelin sheath with WEIGERT's stain, both of which were similar in character to but less predominant in degree than those of the extramedullar spinal roots. In the posterior horns of 2 instances (Cases 2 and 3) the changes mentioned resulted in formation of status spongiosus. The changes in the white matter in the spinal cord were not so apparent. No remarkable signs of inflammatory reactions were observed in the spinal cord, although increase of a small number of glia cells and sparse perivascular collections of a few small round cells were occasionally found. However, neuronophgia was exceptionally found in only one portion of the left posterior horn in the cervical cord in Case 3 (Fig. 13), in which anterior horn of the same side showed only slight chromatolysis and that of the another side remained almost normal (Fig. 12). The leptomeninges displayed generally edema and congestion of the pial blood vessels, and mild degree of leptomeningitis was recognized in some parts of Cases 2, 3 and 5 accompanying infiltration of a small number of lymphocytes and



Fig. 12. Anterior horn cells in the cervical cord in Case 3. The nerve cells are almost normal except slight alteration of NISSL granules.  
NISSL stain;  $\times 460$



Fig. 13. Chromatolysis or dissolution and neuronophagia of the posterior horn cells in the cervical cord. The same section as fig. 12.  $\times 421$

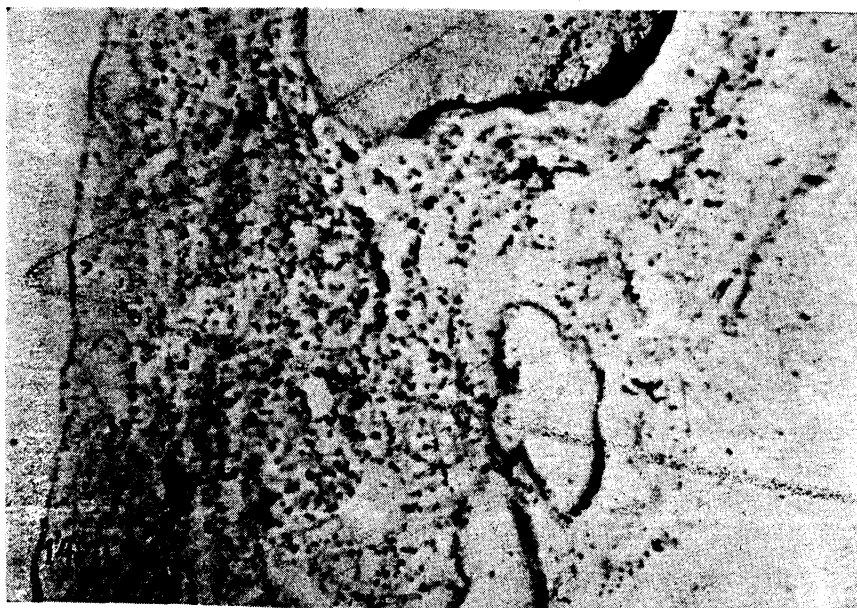


Fig. 14. Thickening of the spinal leptomeninges with engorgement of pial veins as well as focal infiltration of lymphocytes and monocytes and proliferation of pial cells in Case 3.  $\times 103$

occasionally of monocytes and proliferation of a few pial cells (Fig. 14).

3. *The Brains.* The changes were similar to those found in the spinal cord, though less widespread and less intense: there were slight or moderate degree of edema and engorgement of blood vessels (Fig. 15) in all parts of the brains, including

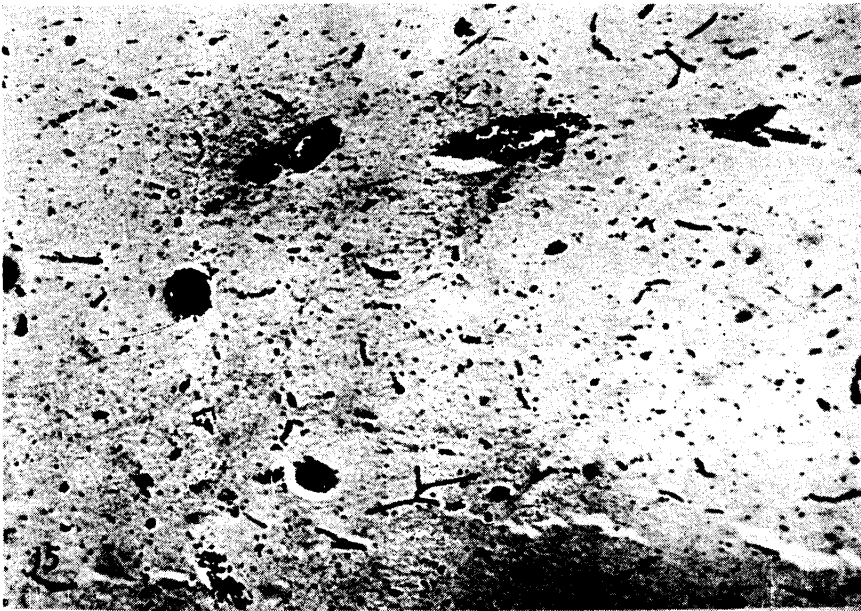


Fig. 15. Engorgement of small blood vessels in the mesencephalon in Case 3. Hematoxylin-eosin stain;  $\times 108$

cerebral leptomeninges, of all cases and small spotty hemorrhages in the cerebral cortex in Case 1. In the cerebrum, as a whole there were neither signs of apparent neuronal alteration nor remarkable glial reaction, though a small necrotic focus with round cell infiltration was encountered in the hypothalamic nucleus of only one instance (Case 2) (Fig. 16), and chromatolysis or neuronophagia by a few glia cells were occasionally found in ganglion-cells of the oculomotorius in Case 3 (Fig. 17), and there were sparse perivascular collections of a few lymphocytes in Cases 2, 3 and 5, which were predominantly in the white matter and subependymal tissues. In the pons and medulla in all instances and in the cerebellum in Cases 1 and 5 slight degree of alteration (central chromatolysis) of some of

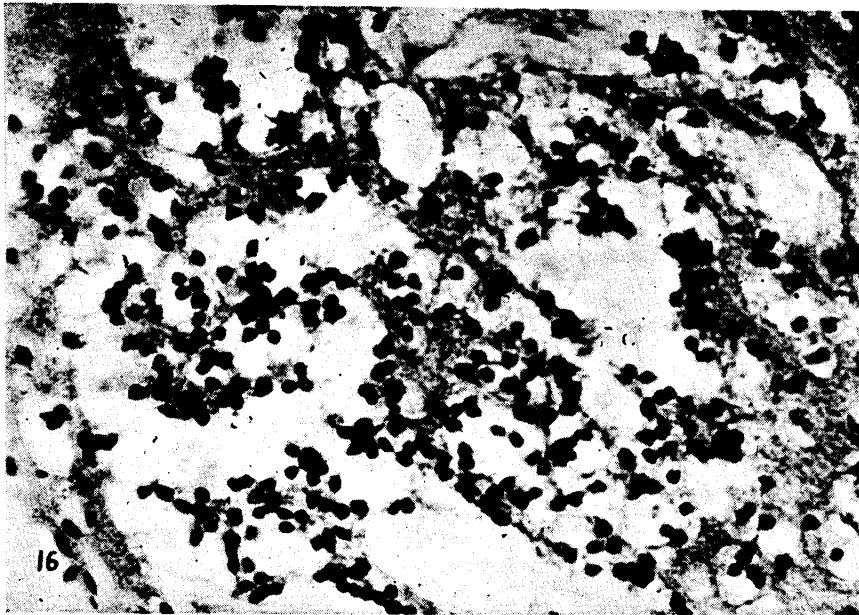


Fig. 16. Small necrotic focus in the hypothalamic nucleus in Case 2. Focal necrosis of nerve cells and fibers with small round cell collections. Hematoxylin-eosin stain;  $\times 338$



Fig. 17. Degeneration of some of nerve cells and glial response in the gray matter of the mesencephalon in Case 3. Nissl stain;  $\times 408$

the nerve cells with the increase of a small number of glia cells scattered along the cranial nerve fibers, and sparse perivascular round cell collections were occasionally found. The changes in the cerebral leptomeninges, which were found in Cases 1 and 5, were slight in degree and similar in character to those of the spinal meninges. In the pachymeninges of Cases 1 and 3 infiltrations of a few monocytes and lymphocytes were found.

4. *Cranial nerves.* Some of the cranial nerves showed a considerable degree of changes similar in character and intensity to those noted in the spinal roots. The kind of the affected nerves varied in each cases : e. g. in Case 2 the most profound changes were encountered in the nerve fibers of the cranial roots of the eleventh (Fig. 18) and the twelveth. Slight alterations of nerve fibers or infiltrations of a few cells were encountered in those of the 2nd, 4th, 5th, 6th, 7th, 8th and 10th ; infiltrations of lymphocytes and a few eosinophiles in the perineurium



Fig. 18 A. Pronounced degenerative changes of nerve fibers of the XIth cranial roots in Case 2. Note the irregular outline and formation of numerous varicosities in some of the swollen axons. BODIAN silver impregnation ;  $\times 315$

Fig. 18 B. Infiltration of lymphocytes and monocytes in the degenerated nerve fibers of the XIth cranial roots in Case 2. Hematoxylin-eosin stain ;  $\times 320$

of the 2nd., a few monocytes in the peri- or endoneurium in the others, moreover hyperplasia of cells of SCHWANN in the 7th.

5. In the peripheral portions of the *autonomous nerves* distributing in the pericardial tissues in Case 2, although the author failed to decide whether they were the sympathetic or the vagus, a remarkable perineuritis of focal type with the collection of a moderate number of lymphocytes happened to be encountered. (Fig. 22)

### B. Other Tissues

The common changes in the viscera of all cases were the moderate degree of engorgement of the small blood vessels, inflammation in the lungs, degeneration of parenchymatous organs such as the liver and kidney, and hyperplasia or follicular atrophy of the lymphatic tissues.

1. *The lung.* The most characteristic change in the viscera was interalveolar pneumonia (interstitial pneumonitis) or com-

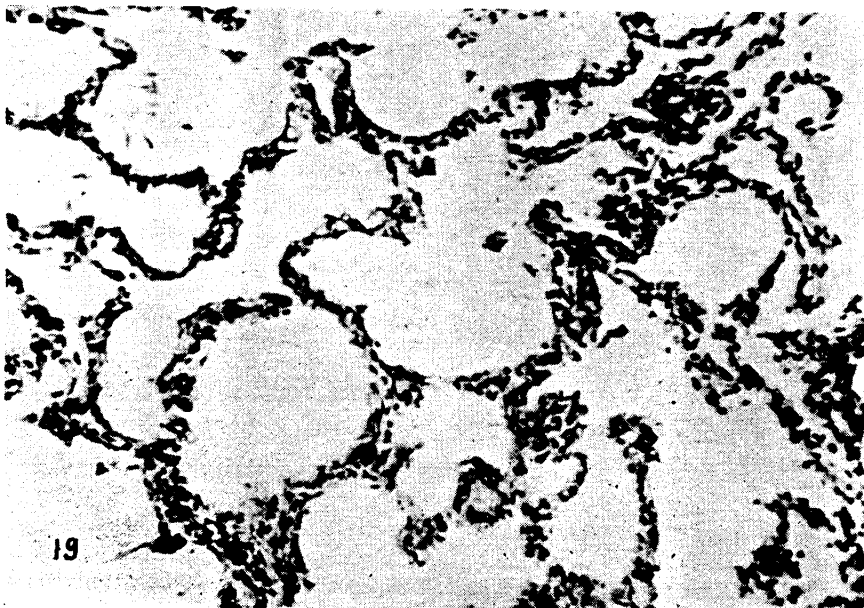


Fig. 19. Interalveolitis of the lung in Case 5. Note the thickening of the interalveolar septa due to proliferation of the capillary wall cells or alveolar lining cells accompanying the infiltration of monocytes, lymphocytes and neutrophils. There is no exudate in the alveolar spaces. Hematoxylin-eosin stain;  $\times 150$

bined type of interalveolar and catarrhalic pneumonia, the former was found most apparently in Cases 5 and 2, the latter in Cases 1, 3 and 4. In the simple type of interalveolar pneumonia the lung represented the thickening of the interalveolar septa with hypertrophia and hyperplasia of the alveolar epithelial cells, accompanying no exudation in the alveolar lumina. In some parts the thickening of interalveolar septa was more advanced with the infiltration of neutrophiles, eosinophiles, monocytes and lymphocytes in the septa (Figs. 19 and 20 in Case 5), and a mass of epithelial cells and mononuclear cells were growing into the alveoli, in which they formed not a few number of giant cells similar to those of WARTHIN-FINKELDEY type and mitosis of mononuclear cells were scattered (Fig. 20, Case 5). Moreover in such alveoli the changes frequently combined bleeding (Cases 4, 2 and 3) or leucocyte exudation, resulting in the development of combined type of interalveolar and hemorrhagic or bronchopneumonia. These changes were quite similar to those of the other viral pneumonia, suggesting

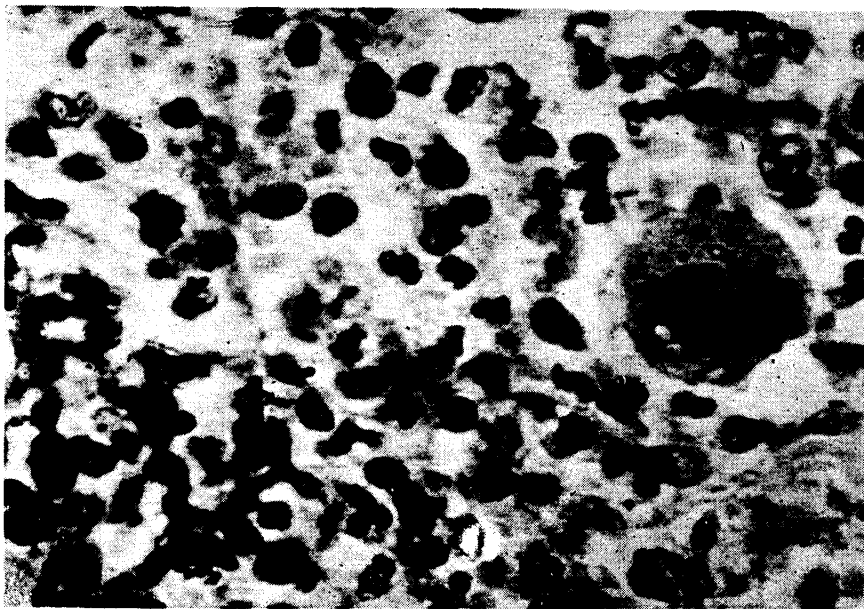


Fig. 20. Advanced thickening of the interalveolar septa with proliferation of septa cells and infiltration of numerous monocytes and lymphocytes and a few neutrophils in Case 5. A mass of epithelial cells and mononuclear cells are growing into the alveoli. Note a giant cell of WARTHIN-FINKELDAY type (right) and a mitotic mononuclear cell (left). Hematoxylin-eosin stain ;  $\times 1,000$

that the present disease might be of viral origin. In addition, congestion and edema of the lungs, predominantly in the lower lobes, were also encountered in the majority of cases, and in some parts hypostatic or aspiration pneumonia was found. These, however, were not characteristic and considered to be of secondary origin.

2. *The heart* showed almost normal appearance except a slight degree of alterations of the muscle fibers in Cases 1, 2 and 3 and perivascular collections of lymphocytes in the interstitial tissues of the myocardium in Case 2, in which collections of lymphocytes were also found around both the small blood vessels and the nerve fibers in the epicardium, which were confirmed by serial sections. (Figs. 21 and 22).



Fig. 21. Slight degeneration of a portion of autonomous nerve fibers distributing in the epicardium and perivascular collection of lymphocytes and monocytes in Case 2. Hematoxylin-eosin stain;  $\times 410$

3. *Skeletal muscle* was available for study in Cases 2 and 3. Myositis of focal type was found scatteringly in some parts of the dorsal muscles in Case 2 (Fig. 23) and of the muscles in the upper thigh of Case 3. The muscle fibers displayed spotty degeneration or necrosis with scanty proliferation of sarcolemmal and interstitial cells and infiltrations of a few monocytes

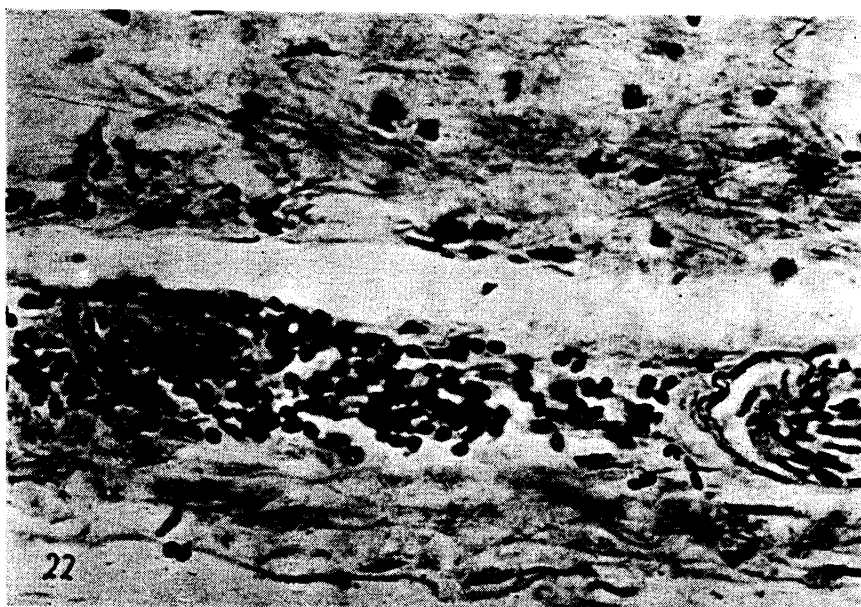


Fig. 22. Focal collection of lymphocytes around a portion (left) of the autonomous nerve distributing in the epicardium in Case 2. Another portion (right) is free from the cell response. Hematoxylin-eosin stain;  $\times 429$



Fig. 23. Focal myositis in the skeletal muscle in Case 2. Degeneration of muscle fibers and collections of a few mononuclear cells. Hematoxylin-eosin stain;  $\times 619$

and occasionally of neutrophils in or around some of the disintegrated muscle fibers.

4. *The liver* showed generally a slight or moderate degree of parenchymatous degeneration. Marked degree of fatty metamorphosis was encountered in Case 2. Periportal accumulation of lymphocytes was noted in Case 2 (Fig. 24) and Case 3.

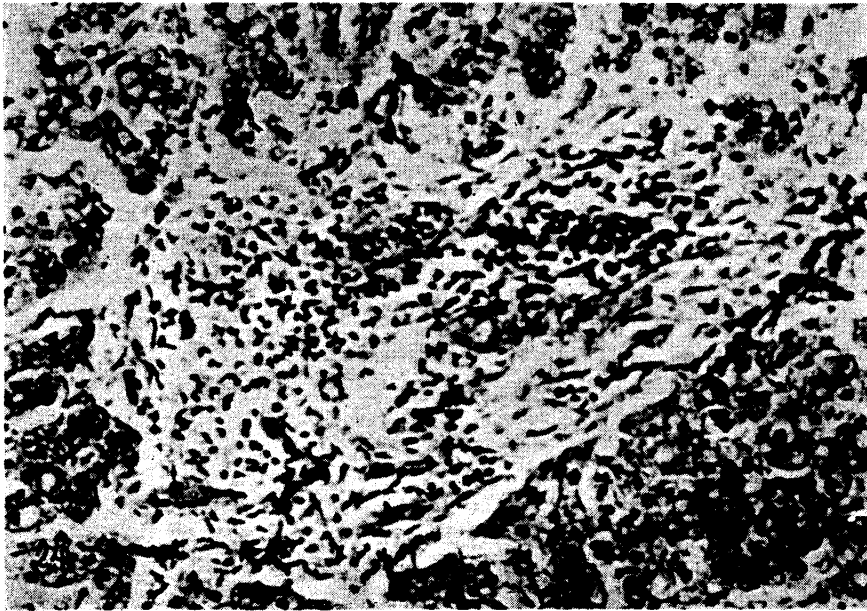


Fig. 24. Periportal accumulation of lymphocytes and moderate fatty metamorphosis and parenchymatous degeneration of liver cells. Hematoxylin-eosin stain;  $\times 297$

5. *The kidney* displayed no marked change, though congestion was conspicuous in general, and a slight or moderate degree of parenchymatous degeneration was seen in the tubular epithelium in all instances.

6. *The spleen.* In the splenic pulps congestion was generally conspicuous, occasionally accompanying bleeding (Case 1 and 2). The folliculi were not conspicuous in boundary, showing atrophy in Cases 1 and 3 or hyperplasia in Case 2. The pulp cells and sinusal endothelial cells showed slight hyperplasia, and some of them appeared in the sinuses. However, no atypical lymphocyte, that frequently appeared in the case of infectious mononucleosis, and no exudative changes were found.

7. *The lymph-nodes* showed similar changes to the spleen;

in Case 1 atrophy, in Case 2 hyperplasia, and in Case 3 subacute lymphadenitis of simple type with hyperplasia of sinusal endothelial cells and appearance in the sinuses of large mononuclear cells, some of which showed phagocytosis of red blood cells.

8. *The bone marrow* appeared almost normal.

9. *The gastrointestinal tract.* Slight degree of catarrhalic or follicular enteritis was encountered with congestion of blood vessels and round cell infiltration in the mucosa in Case 2.

10. *Endocrine organs.* The most remarkable changes was encountered in the adrenal glands. Cortical atrophy was found with decrease in content of lipids in general, slight degree of bleeding in Cases 2 and 4, and occasional degeneration in the zona fasciculata in Case 1 were found.

11. *The other organs.* There were atrophy of Langerhans' islands of the pancreas, round cell infiltration in the interstitial tissues of the pancreas and salivary glands in Case 2 and atrophy of the thyroid gland in Case 4.

### Discussion

In any discussion dealing with pathology of the present disease of unknown etiology, the most important but the most difficult problems seem to be the determination of diagnosis of the disease, whether it is a type of polyradiculoneuritis (Guillain-Barré syndrome) or a type of acute anterior poliomyelitis (Heine-Medin disease), and the clarification of its etiology if it belongs to the former. No definite conclusion may, of course, be hastily drawn from only histopathological investigations of the fatal cases. Nevertheless, we should like to try to discuss briefly here of these problems, basing on its histopathological characteristics of the fatal cases as well as epidemiological and clinical findings of many other non-fatal cases of the present disease<sup>15),16)</sup>.

Polyneuritis in wider sense has so far been considered to be caused by various kinds of etiological agents, such as chemical poisoning, (i. e. alcohol, lead, arsenic, and trichlorethylene), vitamin deficiencies or other metabolic disturbances (i. e. thiamin deficiency, diabetes melitus), bacteria or their toxins (i. e. diphtheria, typhus, pneumonia, scarlatina), and viruses. Since GUILLAIN, BARRÉ and STROHL's<sup>16)</sup> first description

of a type of polyradiculoneuritis "un syndrome de radiculo-névrite avec hyperalbuminose du liquide céphalo-rachidien sans réaction cellulaire" (1916), a large number of similar cases have been reported under a great variety of names. Its etiologic factor has, however, not yet been established, and there exist many discrepancies concerning whether or not it is a disease caused by a specific etiological agent. HAMAMOTO, MIZUTA and KOMAE<sup>19)</sup> of the Pediatrics of our school, who made the epidemiological and clinical observations on fifty cases of the present endemic disease, diagnosed this disease as the Guillain-Barré syndrome or the Landry-Guillain-Barré syndrome, and considered it to be a specific disease of unknown etiology.

The annual numbers of the patients of the present disease diagnosed as GUILLAIN-BARRÉ syndrome in the Pediatrics were as follows: 4 in December of 1949, 33 in 1950, 32 in 1951, 25 in 1952, 12 in 1953, 15 in 1954, and 4 in 1955, totaling 125 as appeared in preface, while those of poliomyelitis were 0 in December of 1949, 15 in 1950, 46 in 1951, 13 in 1952, 59 in 1953, 22 in 1954, and 11 in 1955, totaling 166<sup>18)</sup>. The present disease occurred in every seasons throughout the year mainly in children or infants older than two years of age (average six years of age), while poliomyelitis occurred mainly in the summer months generally in children younger than two years of age. The onset of the present disease was preceded by some symptoms, and about seven or ten days later paralysis occurred suddenly without fever. The prodromal symptoms seen frequently were transitory fever lasting one day or so, discouragement, diarrhea, loss of appetite, tingling, sever pain, disagilitas and others. On the contrary, in polyomyelitis generally the onset of disease began with fever, and paralysis appeared during the febrile period or as it was subsiding. In the present disease the paralysis was widespread mostly beginning from the lower limbs and ascending to the upper and was characterized by a symmetrical bilateral involvement of all extremities and some of the cranial nerves, while in poliomyelitis the paralysis had the tendency to limit itself to isolated muscle groups and was seldom symmetrical, and the involvement of the cranial nerves was rather rare. Sensory disturbances such as severe pain and paresthesia due to the posterior radicular irritation, meningial or vegetative nervous symptoms such as Kernig's sign, nuchal rigidity, hyper-

hydrosis, and dermographismus were conspicuous and continued for a long time in cases of the present disease, while in poliomyelitis those were not always seen and, if seen, slight and continued a short time. Excepting the fatal cases, all cases of the present disease showed a complete recovery from the paralysis with no residual atrophy (*restitutio ad integrum*) from a few months to one year after the onset of the disease, while in many cases of poliomyelitis paralysis remained with muscle atrophy. Finally, observations on the cerebrospinal fluid revealed in most cases of the present disease a slight or moderate increase in the protein content without a concomitant increase in the number of cells (albumino-cytologic dissociation), while in many cases of poliomyelitis there was a moderate or marked increase in cells without a concomitant increase in proteins in their early stage. Concerning all the epidemiological and clinical findings mentioned above, the cases of the present disease is a type of polyneuritis or polyradiculoneuritis quite similar to those of Guillain-Barré syndrome observed by many investigators.

GUILLAIN, BARRÉ and STROHL<sup>16)</sup> stressed the importance of the albuminocytologic dissociation in the spinal fluid and no existence of fatal case in the diagnosis of infectious polyradiculoneuritis. However, in the present disease, as a whole, the increase in the protein content was recognized but not so high as the cases reported as a typical Guillain-Barré syndrome, and yet there were some cases that did not show any albuminocytologic dissociation, though in such cases the other clinical findings were quite similar to those in the Guillain-Barré syndrome. Therefore, as pointed by many investigators<sup>10), 21)</sup>, a great excess of spinal fluid protein and absence of cell increase may not be essential to the diagnosis of Guillain-Barré syndrome<sup>21)</sup>. Moreover, many fatal cases were observed in the present disease as well as in the cases of Guillain-Barré syndrome and infectious polyneuritis reported by many other investigators<sup>21)</sup>. Therefore, it must also be said this disease is frequently fatal. Actually the mortality of the present disease in 1951 was as high as 25 per cent of the patients investigated (HAMAMOTO et al.<sup>19)</sup>).

As regards the fatal cases of the present disease, it might be necessary to compare them with those of Landry's para-

lysis. LANDRY described in 1859<sup>36)</sup> ten cases of acute ascending flaccid paralysis including two fatal cases, in which no histopathological changes were observed in the nervous system, and he believed them to be a specific disease. LEYDEN (1880)<sup>38)</sup> clearly distinguished Landry's ascending paralysis from anterior poliomyelitis. On the other hand, WICKMAN (1905)<sup>64)</sup> observed the similar histopathological changes in autopsy cases of Landry's paralysis as those of poliomyelitis, and advocated that the Landry's paralysis was a type of poliomyelitis. However, this term has been generally applied to acute ascending moter paralysis beginning in the lower limbs and extending upwards until it reaches the respiratory centers, at which stage death might occur. And now it is generally considered to be a symptom complex, and includes cases of ascending type of various polyneuritis or radiculoneuritis, myelitiden and also acute anterior poliomyelitis<sup>29), 30), 64)</sup>. Practically poliomyelitis virus has ever been isolated from some patients who died showing the symptom of Landry's paralysis<sup>29), 30)</sup>. Nevertheless, it is true that there were many cases in which no etiologic agents was detected<sup>37)</sup>. Now, coming to the five fatal cases of the present disease, no essential difference was found in the clinical findings between the fatal and nonfatal cases, except the complete recovery in the latter cases. Moreover, no definite difference was seen in the clinical course and findings between the fatal cases of the present disease and those of Landry's paralysis or bulbar form of poliomyelitis, except the presence of severer pain or sensory disturbances in many cases of the present disease. HAYMAKER and KERNOHAN<sup>21)</sup> believed that Landry's paralysis and Guillain-Barré syndrome represent variations of the same disease entity. They call attention to numerous intermediate cases that bridge the gap between them, and they insisted on using the term "Landry-Guillain-Barré syndrome". HAMAMOTO, MIZUTA and KOMAE<sup>19)</sup> also agreed to this opinion, and diagnosed the present disease as "Guillain-Barré syndrome" formerly and "Landry-Guillain-Barré syndrome" later. Many investigators have believed that these disease should be caused by a certain virus, though the etiology has not been established<sup>5), 16), 33), 37), 50), 52)</sup>. From the foregoing pathologic findings of the five fatal cases of the present disease, it is evident that the primary

and most characteristic feature is the pronounced patchy degenerative changes with slight or moderate inflammatory cell response of focal type of the nerve fibers in the spinal and cranial roots and their peripheral nerves. The distribution of the pathologic changes in the present disease is one of the important marks distinct from the degenerative forms and the atrophic processes, as asserted by KRÜCKE<sup>35),63)</sup>. The cellular infiltration was found even in the cases of early stages such as two or four days' duration of the present disease, as indicated in the cases of infectious polyneuritis by some investigators<sup>5),35),63)</sup>. In the cases of HAYMAKER's observations, however, no degenerative changes accompanied by cellular reactions were found in the early stages before eight days' duration. Moreover, HAYMAKER wrote me in personal communications as follows: "----. Your continued research of fatal cases of the Landry-Guillain-Barré syndrome interests us a great deal because we, too, are continuing to see them, perhaps 60 or 70 since the previous publication appeared. It is still rather rare to find inflammatory cell exudate in early stages, which, I think, makes our cases different from yours in which, as I recall, inflammatory cells were seen rather early. (1956)". "----. From the standpoint of early inflammatory cell response, your cases are highly similar to those I saw in Prof. KRÜCKE's laboratory in Frankfurt some time ago. ----. (1956)". As described in his letters, our cases are quite similar to those reported by K. WEISSE<sup>63)</sup> and W. KRÜCKE<sup>35)</sup>; die tödliche „primär-entzündliche“ Polyneuritis im Kindesalter. In the ventral cornua of the spinal cord in our cases no such conspicuous inflammatory changes were recognized as those which are usually encountered in typical cases of acute anterior poliomyelitis. Slight or moderate degree of degenerative changes were found in both the ventral and dorsal cornua as well as intermediate gray in the spinal cord and also in the white and gray matter of the medulla and brain stem, some of which were considered to be the retrograde degeneration and others probably to be the primary affection. In one instance, Case 3, which showed the symptom of diplopia, chromatolysis and rare neuronophagia were found in ganglion cells which belong to the oculomotorius and those of the posterior cornua in the cervical cord, in which the anterior cornua of the same segment appeared almost normal. Moreover,

in Case 2, a small necrotic focus with inflammatory cell response was found in the hypothalamic nucleus, while no inflammatory change was recognized in the anterior cornua of the spinal cord. Therefore, the lesions in the peripheral nervous system coincide with those of infectious polyneuritis, although those in the central nervous system may not permit to deny definitely a type of Landry's form or bulbular form of poliomyelitis. Moreover, the changes in the dorsal root ganglia are similar to those in the cases of infectious polyneuritis and poliomyelitis reported by DORING<sup>7)</sup> and STAEMMLER<sup>57)</sup>, and the changes of the autonomous nerves are similar to those of PERTERS and SCHEID<sup>50)</sup>. Judging from the entire histopathologic changes in the nervous system demonstrated above, our cases are diagnosed as encephalomyelopolyradiculoneuritis<sup>39)</sup>.

Concerning the etiology of the present disease some investigations were made, failing to yield any data for the establishment of the definite etiologic factor of the disease. FUJIWARA, KANZAKI, KANATANI and KOMAE (1952)<sup>12)</sup> carried out immunologic studies on the present disease by neutralization test for the Lansing strain of poliomyelitis virus, but any definite relationship between poliomyelitis virus and the present disease was not drawn from their results. Moreover, any poliomyelitis virus was not isolated from the patients of the present disease<sup>18)19)</sup>, and there were some patients, though few in number, who had no antibody against any poliomyelitis viruses (Prof. HAMAMOTO)<sup>18)</sup>. These data may show that the present disease is etiologically different from poliomyelitis. FUJIWARA and KOMAE (1952)<sup>11)</sup> isolated two strains of Cocksackie virus from the feces of two patients of the present disease respectively, one of which (Okumoto strain ; Cocksackie virus type A 19) was from Case 2 in the present necropsy cases. The suckling mice inoculated with the saline solution of the feces showed flaccid paralysis of the extremities and died a few days after the onset of the symptom. The transmission of the disease by the inoculation of muscle emulsion from these mice to the others was always successful in producing the same clinical pictures. T. ODA<sup>46)</sup>, one of us, carried out the experimental studies on the histopathologic changes of suckling and young mice inoculated with some strains of neurotrophic viruses such as Cocksackie virus (High point and Connecticut 5), Lansing strain of poliomye-

litis virus, Japanese encephalitis virus and Columbia SK virus. However, etiological relation between the Cocksackie viruses and the present disease has not yet been established. Concerning the relationship between Cocksackie viruses and infectious polyneuritis, there exists also the discrepancy of opinions among many other investigators<sup>6), 41), 18)</sup>, and most of the data are negative.

Recently, some investigators have suspected sensitivity or allergy and vitamin deficiency<sup>17), 27)</sup> or disturbance of enzyme metabolism of neurons as the causative factors of a type of polyneuritis or Guillain-Barré syndrome. Allergy theory was advocated for the first time in the Landry's paralysis by GRÜNEWALD (1923)<sup>16)</sup>, and in polyneuritis with the Guillain-Barré's syndrome by BALDUZZI (1938)<sup>3)</sup>, PETTE (1942), BANNWARTH (1943) and EDERLE (1947)<sup>8)</sup>. BANNWARTH (1948)<sup>4)</sup> observed 5 cases of a typical polyneuritis with the Guillain-Barré syndrome in 8 cases which occurred after typhus and paratyphus-vaccination. This fact may suggest the existence of some cases of allergic origin in a type of polyneuritis with the Guillain-Barré syndrome at least. FANCONI (1950)<sup>9)</sup> explained the encephalomyelo-radiculoneuritis as neuro-allergic manifestation. WACKSMAN and ADAMS (1955)<sup>62)</sup>, who made the experimental studies on allergic neuritis of rabbits induced by the injection of peripheral nervous tissues and adjuvants (tuberculous bacilli-containing wax), indicated the similarity between this noninfectious experimental allergic neuritis and a certain human polyneuritis. Therefore, we can not deny the possibility of the occurrence of polyneuritis of non-viral allergic origin. However, from the view-point of epidemiological and clinical findings, the present endemic disease is considered to be infectious, and from our histopathological observations, especially from the inflammatory changes of focal type and their distribution, it may be considered to be of viral origin, probably due to a type of panneurotropic and viscerotropic virus similar to but somewhat different in characters and in its affecting areas from poliomyelitis viruses; by some possibility the virus might be a variant<sup>65)</sup> of polio virus, and/or participation of allergy or parallergy<sup>65)</sup> might have played an important rôle in the development of the changes of the present disease.

Concerning the explanation of some of the clinical symptoms basing on the morbid anatomy, the view expressed by

SCHEINKER<sup>56)</sup> is accepted as reasonable that the acute or subacute development of a flaccid paralysis of the extremities is due to a sudden increase in the bulk of most of the spinal roots, resulting in strangulation and mechanical constriction of the radicular nerves at their point of penetration of the spinal meninges. Complete recovery from paralysis without any residual atrophy is explained by no existence of advanced necrosis of ganglion cells in the anterior horn of the spinal cord. High degree of pain and sensory disturbances are explained by the involvement of the posterior roots and ganglion cells. Bulbar symptoms such as dyspnea and dysphagia are associated with the involvement of the bulbar nerves and cervical and thoracal nerves. Respiratory failure, which could usually be traced to bulbar or intercostal paralysis and might be accelerated by the complication of pneumonia, is regarded as the final event in the great majority of the cases.

Many cases of the present endemic disease are still occurring in these regions. In order to find out the true etiologic agent, further comprehensive investigations of the disease, experimental studies in particular, are necessary.

### Summary

Histopathological investigations were carried out on five fatal cases of a type of polyneuritis of unknown etiology diagnosed as Landry-Guillain-Barré syndrome, which endemically occurred in children in the regions surrounding the Inland Sea of Japan.

The most characteristic pathologic feature in the nervous system was pronounced patchy degenerative changes with slight or moderate degree of inflammatory cell response of focal type in the peripheral and cranial nerves, predominantly in the nerve fibers of the spinal and cranial roots. In the spinal cord, medulla, pons, and in some portions of the cerebrum and cerebellum, engorgement of the small blood vessels as well as edema and the less predominant scattered degenerative changes of ganglion-cells and nerve fibers with extremely slight degree of glial response and sparse perivascular cell collections were encountered. The cerebrospinal meninges displayed edema and congestion of the pial blood vessels with focal collections of a small number of lymphocytes and/or monocytes. No advanced involvement of the anterior horn of the spinal cord in a strict sense of anterior

poliomyelitis was, however, recognized. These changes may lead the histopathologic diagnosis of the present disease to infectious encephalomyelo-polyradiculoneuritis or a type of infectious polyneuritis.

The main histopathologic changes in the visceral organs were a moderate degree of engorgement of the small blood vessels, degeneration of parenchymatous organs such as the liver and kidney, hyperplasia or follicular atrophy of the lymphatic tissues, interalveolar pneumonia, focal myositis, and slight degree of round cell infiltrations in the interstitial tissues of the other viscera, such as the liver, heart, and gastrointestinal canal.

Based upon the observations on the histopathological changes as well as clinical manifestations, discussions were made on the pathogenesis and etiologic factor of the present endemic disease with critique on the literatures.

*Acknowledgment* : We wish to express our sincere gratitude to Professor emeritus Dr. HIROSHI TANABE, Professor Dr. SATIMARU SENO and Professor Dr. YUKIO HAMAZAKI, Dept. of Pathology, Okayama University, for their invaluable advice and encouragement. Our grateful thanks are due to Professor Dr. EIJI HAMAMATO, director of the Dept. of Pediatrics of our School, for supplying the clinical data in this study, and to Professor Dr. MASASHI MIYAKE, Dept. of Pathology, Tokyo University, and to Dr. MASAMI KITAOKA, director of the Viral and Rickettsial Department of the National Institute of Health, for their generous welcome and great kindness. We are indebted to Dr. WEBB HAYMAKER, of the Army Institute of Pathology, Washington, Professor Dr. KARLA WEISSE, of the University-Childrenclinic Frankfurt a. M. and Professor Dr. WILHELM KRÜCKE, of the Neurological Institute of Frankfurt a. M. University, not only for their useful criticism, but also for their interest and encouragement. Thanks are also due to Dr. YOSHIO SUGIHARA, Dr. IKURO MURAKAMI and Dr. MITSUO TANI for their co-operation in autopsy and to Mr. YUTAKA KUYAMA for his technical assistance.

## References

- 1) ACCORNERO, F.: Zur Frage der Rückenmarksveränderungen bei Polyneuritis. Dtsch. Z. Nervenheilk. **143**, 137—157, 1937. — 2) AKAGI, S.: An autopsy case of Landry-Guillain-Barré syndrome (Abstract ; in Japaese). Tr. Soc. Path. Jap. **41**, (Ed. reg.), 190—192, 1952. — 3) BALDUZZI, O.: Anatomia pathologica dela "polyradiculitis acuta curabilis" con dissociatione albumino-citroica, Syndrome di Guillain-Barré. Riv. Pat. nerv. **51**, 288—312, 1938. — 4) BANNWARTH, A.: Neuritis und Polyneuritis nach Typhus und Paratyphus-Schutzimpfung. Ein weiterer Beitrag zum Thema, "Allergie und Nervensystem." Arch. f. Psychiatr. u. Z. Neur. **180**, 531—568, 1948. — 5) BOGAERT, L. VAN: Sur la polyradiculonévrite ascendante subaiguë avec dissociation albumino-cytologique à évolution mortelle. (Remarques histopathologiques et nosologiques.). Mschr. Psychiatr. **104**, 129—149, 1941. — 6) DALLDORF, G. and SICKLES, G. M.: An unidentified, filtrable agent isolated from the feces of

children with paralysis. *Science*, **108**, 61, 1948. — 7) DÖRING, G.: Pathologische Anatomie der Spinal- und Hirnnervenganglien, einschließlich der Wurzelnerven. *Handbuch der Speziellen Pathologischen Anatomie und Histologie* von O. LUBARSCH, F. HENKE, und R. RÖSSLE. **13/5**, 249—356, 1955. — 8) EDERLE, W.: Allergie und Nervensystem. *Beih. Z. Med. Wschr.* 1947, Nr. **3**. — 9) FANCONI, WALLGREN: Polyradiculitis. *Lehrbuch der Pädiatrie*, 1950. — 10) FEER, : Veränderungen des Liquor cerebrospinalis bei diphtherischen Lähmungen. *Dtsch. med. Wschr.* **1**, 967, 1910. — 11) FUJIWARA, H. and KOMAE, T.: Two strains of virus isolated from the feces of "Landry-Guillain-Barré's syndrome" patients pathogenic for suckling mice. (in Japanese) *Virus*, **3**, 32—39, 1953. — 12) FUJIWARA, H., KANZAKI, K., KANATANI, T. and KOMAE, T.: Immunologic studies on "Landry-Guillain-Barré's syndrome". (in Japanese) I. Neutralization test for the Lansing strain of poliomyelitis virus. II. Hemagglutination inhibition test of New Castle virus with human O-type erythrocytes. *Virus*, **3**, 27—31, 1953. — 13) FUKUMI, H and YOKOTA, T.: Etiological studies on Coxsackie virus disease. (in Japanese) *Jap. Jour. of Med.* **1455**, 20, 1952. — 14) GOTO, T.: On Guillain-Barré syndrome. (in Japanese) *Shinryo Igaku*, **9**, 15—20, 1950. — 15) GRÜNEWALD, E. A.: Studien zur pathologischen Anatomie der "Landry'schen Paralyse". *J. Psychol. u. Neur.* **29**, 55—92, 1922. — 16) GUILLAIN, G., BARRÉ, J. A., and STROHL, A.: Sur un syndrome de radiculo-névrite avec hyperalbuminose de liquide céphalo-rachidien sans réaction cellulaire. Remarques sur les caractères cliniques et graphiques des réflexes tendineux. *Bull. et mém. Soc. méd. d. hôp. de Paris*, **40**, 1462, 1916. — 17) VON HAGEN, K. O. and BAKER, R. N.: Infectious neuronitis, present concepts of etiology and treatment. *Jour. of A. M. A.* **151**, 1465—1471, 1952. — 18) HAMAMOTO, E.: On a type of polyneuritis which shows Guillain-Barré syndrome. (in Japanese). Presented at the 59th General Meeting of Japan Pediatric Society at Okayama on May 14th, 1956. — 19) HAMAMOTO, E., MIZUTA, K. and KOMAE, T.: Clinical and epidemiological observations on fifteen cases of Guillain-Barré syndrome. (in Japanese). *Jika-shinryo*, **15**, 215—223, 1952. — 20) HALLERVORDEN, J.: Encephalitis und Polyneuritis. *Nervenarzt* **16**, 417—428, 1943. — 21) HAYMAKER, W. and KERNOHAN, T. W.: The Landry-Guillain-Barré syndrome. A clinicopathologic report of fifty fatal cases and a critique of the literature. *Medicine*, **28**, 59-141, 1949. — 22) HINO, S.: Primary polyneuritis. (in Japanese). *Shindan to chiryo*. **29**, 1194, 1942. — 23) HORITA, M., KASHIWAGI, O. and AKUTAGAWA, S.: On the Guillain-Barré syndrome. *Rinsho to Kenkyu*. **27**, 248, 1950. — 24) HOWE, H. A.: In *Viral and Rickettsial Infections of Man*, by T. M. RIVERS. 300—337, T. B. Lippincott Co., 1952. — 25) IWAZAWA, K.: Cases of polyneuritis in children. (in Japanese). *Shonika Rinsho*, **3**, 3—15, 1950. — 26) JACOBI, H. G.: Infective neuronitis. Report of a case with autopsy observations. *Arch. Int. Med.*, **48**, 764, 1931. — 27) JOINTER, G. L., MCARDLE, B., and THOMPSON, R. H. S.: *Brain* **73**, 431, 1950. — 28) JONES, T. A., HOLMES, J. W. and WEINSTEIN, M.: Acute infectious polyneuritis (Guillain-Barré syndrome). A brief review of the literature with report of 3 cases. *Am. J. M. Sc.*, **206**, 305, 1943. — 29) KASAHARA, M., OGATA, S., KATO, T. and TOMITA, T.: Supplements to the findings on Landry's paralysis. *Jour. Osaka Med. Ass'n.* **41**, 1105—1121, 1942. — 30) KAWAMURA, R., KASAHARA, S. and YAMADA, R.: Demonstration der histologischen Präparate bei der menschlichen und experimentellen Poliomyelitis anterior. *Tr. Soc. Path. Jap.* **29**, 118—119, 1939. — 31) KITAMURA, K. and ITO, K.: On the Guillain-Barré syndrome. *Rinsho Naika Shonika*, **7**,

- 305, 1952. — 32) KITAOKA, M.: On classification of poliomyelitis virus and epidemiological study of poliomyelitis. *Virus*, **2**, 48—58, 1952. — 33) KOLLE, K., G. SCHALTENBRAND u. Fr. TÖBEL: Zur Frage der infektiösen Polyneuritis. *Dtsch. Z. Nervenheilk.* **167**, 215—236, 1952. — 34) KOMAE, T., FUJII, C. and HACHIYA, R.: The isolation of a Coxsackie virus from two sporadic cases of epidemic pleurodynia. *Virus*, **5**, 213—219, 1955. — 35) KRÜCKE, W.: Die primär-entzündliche Polyneuritis unbekannter Ursache. *Handbuch der speziellen pathologischen Anatomie und Histologie*, von O. LUBARSCH, F. HENKE und R. LÖSSLE. **13/5**, 164—182, 1955. — 36) LANDRY, O.: Note sur la paralysie ascendante aiguë. *Gaz. hebdomadaire de médecine*, **6**, 473—486, 1859. — 37) LESCHKE, E.: Über den Erreger der Landry'schen Paralyse. *Berl. klin. Wschr.* **51**, 783, 1914. — 38) LEYDEN, E.: Über Poliomyelitis und Neuritis. *Ztschr. f. klin. Med.*, **1**, 387, 1880. — 39) MARGULIS, M. S.: Pathologie und Pathogenese der akuten primären infektiösen Polyneuritiden. *Dtsch. Z. Nervenheilk.* **99**, 165—192, 1927. — 40) MARINESCO, G.: Des polynévrites en rapport avec les lésions primitives et secondaires des cellules nerveuses. *Revue neur.* **4**, 129—141, 1896. — 41) MELNICK, J. L.: Studies on the Coxsackie viruses: Properties, immunological aspects and distribution in nature. *Bull. N.Y. Acad. Med.*, **26**, 342, 1952. — 42) MIZUTA, K.: On acute infectious polyneuritis in children, prevailing in this winter. Statistical observations of ten cases. (in Japanese). *Jika-shinryo*, **14**, 37—42, 99—103, 1951. — 43) MURAKAMI, K.: On Guillain-Barré syndrome in children clinic. (in Japanese) *Jika-shinryo*. **12**, 127, 189, 240, 1948. — 44) MURAKAMI, U. and OTSUKI, N.: A typical case of Guillain-Barré syndrome found in Japan. (in Japanese). *Seishin-shinkeigaku Zassi*. **45**, 161, 1941. — 45) NAKATANI, M. and NISHIMURA, K.: A case of acute primary infectious polyneuritis. (in Japanese) *Seishin-shinkeigaku Zassi*. **41**, 1—12, 1937. — 46) ODA, T.: Histopathologic changes in suckling mice inoculated with Coxsackie virus. (Abstract in Japanese). *Okayama Igakkai Zassi*, **65**, (2), 58—59, 1953. — 47) OGATA, S., TOMITA, T. and SATO, H.: Study on Landry's paralysis. (in Japanese). *Byorigaku Zassi*, **1**, 326—336, 1942. — 48) OKANO, K. et al.: Pathology of Landry's paralysis in humans (Report No. 1, Particularly on changes of digestive tract) (in Japanese). *Tr. Soc. Path. Jap.* **40**, (Ed. regionalis), 255—258, 1951. — 49) OKANO, K. et al. Structural changes of various organs in Heine-Medin's disease (Report II). *Tr. Soc. Path. Jap.* **41**, 440—444, 1952. — 50) PETERS, G. and SCHEID, W.: Zur Klinik und Anatomie der nach Typus der Landry'schen Paralyse verlaufenden Polyganglio-radikulitis-neuritis. *Zeitschr. f. d. ges. Neurol. u. Psychiat.* **163**, 367, 1938. — 51) PETTE, H.: Das Problem der Neuritis. *Verh. dtsh. Ges. inn. Med.* **55**, 92—136, 1949. — 52) PETTE, H. und KÖRNEY, S.: Zur Histologie und Pathogenese der akut-entzündlichen Formen der Landry'schen Paralyse. *Zeitschr. f. d. ges. Neurol. u. Psychiat.* **128**, 390, 1930. — 53) SABIN, A. B. and CHARLES, D. A.: Visceral lesions in infectious polyneuritis. (Infectious neuronitis, acute polyneuritis with facial diplegia, Guillain-Barré syndrome, Landry's paralysis.) *Amer. J. Path.* **17**, 469—482, 1941. — 54) SANDERS, M., ALFRED B., CORAL G. and HAYMAKER W.: Polyradiculopathy in man produced by St. Louis encephalitis virus (SLE). *South. Med. J.* **46**, 606—608, 1953. — 55) SCHEINKER, I. M.: Pathology and pathogenesis of infectious polyneuritis (Guillain-Barré syndrome). *Jour. Neuropathol. and Exper. Neurol.* **8**, 184—193, 1949. — 56) SENATOR: Über akute Polymyositis und Neuromyositis. *Dtsch. med. Wschr.* **19**, 933, 1893. — 57) STAEMMLER, M.: Die Spinalganglien und Rückenmarkswurzeln bei Poliomyelitis und Polyneuritis. *Klin. Wschr.* **27**, 56—59, 1949. — 58) SUGIHARA, Y., ODA, T.,

MURAKAMI, I. and TANI, H.: Four autopsy cases of Guillain-Barré syndrome. (Abstract; in Japanese). Okayama Igakkai Zassi, **63**, 230, 1951. — <sup>59)</sup> TAKEISHI, H.: Polyneuritis. (in Japanese). Grenzgebiet, **13**, 1280—1284, 1939. — <sup>60)</sup> TANABE, H., SUGIHARA, Y. and ODA, T.: Histologic changes of the lung in Guillain-Barré syndrome. (Abstract; in Japanese) Tr. Soc. Path. Jap., **40**, (Ed. regionalis), 258—259, 1951. — <sup>61)</sup> TASHIRO, T.: Guillain-Barré syndrome. (in Japanese). Hokkaido Igaku Zassi, **20**, 1450. 1942. — <sup>62)</sup> WAKSMAN, B. H. and ADAMS, R. D.: Allergic neuritis; an experimental disease of rabbits, induced by the injection of peripheral nervous tissue and adjuvants. Jour. of Exp. Med. **102**, 213—236, 1955. — <sup>63)</sup> WEISSE, K. und KRÜCKE, W.: Die tödliche "primär-entzündliche" Polyneuritis im Kindersalter. Zeitschr. f. Kinderheilk. **74**, 167—208, 1954. — <sup>64)</sup> WICKMAN, O. I.: Acute poliomyelitis. Nervous and Mental Disease Monograph Series No. 16, New York, J. Nervous and Mental Disease Pub. Co. 1913. — <sup>65)</sup> SABIN, A. B.: Pathogenesis of poliomyelitis. Science, **123**, 1151—1157, 1956.

---