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PATHOLOGICAL STUDIES OF MAREK'S DISEASE

I THE HISTOPATHOLOGY ON FIELD CASES IN JAPAN

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In order to clarify the characteristics of Marek's disease, 181 cases of chickens were histopathologically investigated. They consisted of field cases which were considered as cases of classical (groups A, B & C) and acute Marek's disease (groups D, E & F) on the basis of clinical, epidemiological and pathological features.

As a result of investigation, basically 2 kinds of lesions were found in the peripheral nerves: Tumorous proliferation (T-type) and non tumorous response (R-type). Therefore, each case consisted of any of 3 types (T, T+R, R).

Furthermore, T-type lesions could be subdivided into 3 according to the types of cell which appeared and the characteristics of the lesions. T_I-type lesions consisted of only uniform small lymphoid cells. T_{II}-type lesions consisted of pleomorphic cells which included small, medium and large lymphoid cells (lymphoblastic and hemocytoblastic) and fewer reticulum cells. T_{III}-type lesions consisted of reticular or undifferentiated mesenchymal cells.

R-type lesions of small lymphocytic and plasma cellular infiltration and were accompanied by frequent edema and proliferation of Schwann cells.

Tumorous proliferation was often found in the visceral organs and tissues, and the central nervous system. The cells of which they were composed were similar to those of the peripheral nerves (T_I, T_{II}, T_{III}). Tumorous invasion was found extending from the nerve fibers in the visceral organs and tissues to the adjoining tissues in some places. Eye lesions were considered as one kind of lesion in systemic tumorous proliferation.

All investigated groups were regarded as one disease entity with lesions possessing the same characteristics, but of varying severity.

Consequently, it may be considered that Marek's disease is closely connected with the nerve tissues and the lesions mainly consisted of tumorous proliferation of lymphoreticular cells originating from the undifferentiated mesenchymal tissues of the extracapillary reticular tissues in the whole body.

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INTRODUCTION

Marek's disease is a common lymphoproliferative disease of chickens affecting the peripheral nerves, other tissues and visceral organs. The name "Marek's disease" was first proposed by BIGGS (1961) and was regarded as synonymous with "fowl paralysis" or "neurolymphomatosis,"[31,32] which were well known.

Marek's disease was originally described by MAREK (1907) in four adult cockerels with leg paralysis in Hungary. He called it polyneuritis. After that, PAPPENHEIMER et al.[31,32] reported an association of lymphoid tumors in the peripheral nerves as well as visceral organs and used the name "neurolymphomatosis gallinarum." At that time, Marek's disease had been considered as a different disease from lymphatic leukosis (lymphoid leukosis) by ELLERMANN (1922). However, the difficulty in differentiating the lymphoid tumors of lymphoid leukosis from those associated with Marek's disease led to the adaptation of the term "avian leukosis complex" which was proposed by JUNGHERR[1], and later modified by COTTRAL. In this classification, these two diseases were grouped as a single pathological condition under the term "neural and visceral lymphomatosis." The use of this term was interesting as it implied unintentionally that two diseases were caused by the same etiological agent. BIGGS[5] and CAMPBELL[8,9] made a plea for a new classification of this "avian leukosis complex," from the epidemiological and pathological evidence. They considered that lymphoid leukosis and Marek's disease were two distinct and unrelated diseases. This opinion was adopted at the First Conference of the World Veterinry Poultry Association[5]. It was decided to discard the term "lymphomatosis" because of confusion and to name the disease originally described by MAREK and called "neurolymphomatosis" by PAPPENHEIMER et al.[32], "Marek's disease."

On the other hand, with the rapid progress of recent etiological studies, the avian leukosis complex has been divided into two groups according to etiology[7]; the leukosis/sarcoma group (included lymphoid leukosis) and the Marek's disease group. The former is caused by a RNA type virus (leukovirus) and positive in RIF and COFAL tests. The etiological agent of the latter is strongly suggestive of a DNA type virus (a group B herpes virus[28]) and Marek's disease is negative in RIF and COFAL tests. Lymphoid leukosis and Marek's disease, therefore, are considered as separate entities in etiology.

BENTON & COVER (1957) reported an increased incidence of "visceral lymphomatosis" in the U.S.A. in broiler and replacement birds, eight to ten weeks of age. This kind of disease had been occurring since 1949 according to these authors. The disease was characterized by an unusually high rate of incidence and mortality in a flock and a high incidence of lymhoid tumors in the visceral

organs. An apparently similar disease was also observed in England (1965)[6]. BIGGS[5] named the disease as "acute Marek's disease" on the basis of transmission experiments and studies of the condition in the field, and called "fowl paralysis" or "neurolymphomatosis" as "classical Marek's disease." Classical and acute Marek's disease, however, are considered fundamentally to be the same disease, except for differences in the degree of severity.

Marek's disease in Japan was reported formerly by EMOTO & MIYAMOTO (1930), recently FUJIMOTO & NAKAGAWA (1964), NAKAGAWA (1964) and YAMAGIWA et al. (1964, 1967) under the name "fowl paralysis." During the past few years, increased incidence of a disease which was considered as acute Marek's disease, has been reported by several workers[18,21,43]. Marek's disease is becoming a menace to the poultry industry owing to the serious economic loss it causes. Studies of Marek's disease are now starting on a full scale, though a little too late in Japan.

The present authors are not always satisfied with the present name of Marek's disease and classification of avian leukosis, but we will use this term in this communication in view of the present state of the studies of Marek's disease in the world. In this present study, we investigated field cases which were considered to be cases of Marek's disease during the last decade, and tried to clarify the characteristics of the lesions of the disease from the view point of patho-morphology.

MATERIALS AND METHODS

Investigated chickens consisted of field cases which were considered as cases of classical (groups A, B & C) and acute Marek's disease (groups D, E & F) on the basis of clinical, epidemiological and pathological features. These chickens were selected histopathologically from cases showing lymphoid cell infiltration or proliferation in the peripheral nerves. In the investigated groups the number of cases and year of collection were as follows: group A 59 cases, 1959~63; group B 12 cases, 1962~63; group C 60 cases, 1967~68; group D 31 cases, 1967; group E 15 cases, 1968; group F 4 cases, 1969 (table 1). Groups A, B & C were collected from many parts of Hokkaido. Groups D, E & F were collected one each from poultry in Ebetsu, Takikawa and Shimizu Hokkaido respectively. The breeds in groups A, B & C consisted mainly of White Leghorn, and the others were New Hampshire, Hacco Brown, AA-56 and Rhode Island Red. Ages ranged from 40 to 730 days (most of them were 40 to 180 days). The breeds in groups D, E & F consisted of White Leghorn and ages ranged from 73 to 182 days.

Clinical signs were fully observed in all cases before depletion of blood, except in a few cases where death had already occurred. After post-mortem examinations, materials were fixed in 10% formalin. As many blocks of tissues as possible were collected from various parts of the organs and nerve tissues as a rule, but in groups A and D, only restricted parts of the nerve were examined. The brain and eye were only examined in

groups A and B. Paraffin sections were stained mainly with hematoxylin-eosin. LUXOL-fast blue and HEIDENHEIN-WOELKE for staining myelin, BODIAN's impregnation method for neurofibrils, MALLORY's Azan stain of HEIDENHEIN modification were utilized on some of the materials.

RESULTS

Clinical findings

Groups A, B & C Torticollis (4 cases in group A), drooping of the wings, paresis of the legs or wings on one side or both, inward curving of the toes, weakness of the legs and a squatting position which were regarded as indications of nervous disturbances of the neck, wings or legs were observed. Characteristic respiratory symptoms (gasping) which may indicate disturbances of the vagus were also found (5 cases in group A). A circulating movement with torticollis was detected in 2 cases of group B. Symptoms in the neck or wings were usually associated with the symptoms in the legs, but the incidence of the former was relatively low, that of the latter being higher. According to the notes taken, cases which revealed respiratory symptoms in group A were all from the same poultry farm and from the same period when the disease was prevalent. At the begining, respiratory symptoms appeared and a sudden onset of paralysis became aware by a difficulty or inability in walking. On the other hand, partial or complete blindness in one or both eyes, accompanied by distortion of the pupils, depigmentation (silver or grey eyes) and iritis were observed in several paralysed chickens (8 cases in group A, 2 cases in group B). Among 20 cases showing severe paralysis of the legs in group C, 15 cases were accompanied by drooping of the wings.

Groups D, E & F All cases were collected each from one poultry farm during on same outbreak and an unusually high rate of incidence and mortality was shown. Most of the affected chickens showed a depressed condition, and some of them showed anemia, emaciation, diarrhea and excretion of green feces. Drooping of the wings was found frequently. In most of the cases, paralytic symptoms of the legs were not conspicuous, and only a few showed abnormal reflex and sensation.

Macroscopic changes

Groups A, B & C The peripheral nerves of most of the affected cases showed swelling, edema, loss of striation and discoloration. The most commonly affected parts of the peripheral nerves were as follows: The brachial plexus and their dorsal root ganglia, the lumbosacral plexus and their dorsal root ganglia, and the vagosympathetic trunk. Proximal parts of the peripheral nerve were affected in high incidence. At the same time, macroscopically lymphoid tumors were often observed in the visceral organs: group A 11.9% (7/59); group B 25.0% (3/12); group C 21.7% (13/60). Distribution of the lymphoid tumors in the visceral organs were listed as chart 1: particularly involving the proventriculus, lungs, serosa, liver, ovary and kidneys. In one case out of 4 with torticollis in group A, a bean-sized white tumorous mass ranging from the areas of the thalamus to the small brain and medulla oblongata was found. In the other case with torticollis, a tumorous

mass, 0.5×3 cm in size, was found at the vagus two-thirds of the way up the neck. In one case out of 2 accompanied by a circulating movement and torticollis in group B, a tumorous mass was observed at the vagus of the neck. A nephroblastoma was found in one case of group B.

Groups D, E & F In these groups, lymphoid tumors in the visceral organs were macroscopically observed in high incidence; group D 58.1% (18/31); group E 80.0% (12/15); group F 100.0% (4/4). Distribution of the lymphoid tumors in the visceral organs was listed as chart 2; particularly involving the ovary, liver, spleen, proventriculus, lungs, adrenals and kidneys. Grey-white nodular tumors were observed sporadically or multiply in the various organs. Some of the tumorous masses were ill-defined and had a diffuse reticular appearance. Enlargement of the bursa of Fabricius was found only in one case each in groups E and F. The lesions of the peripheral nerves were not as conspicuous as those of the visceral organs in these groups.

Microscopic changes

Peripheral nerves

Classification of the type of lesions Lesions in the peripheral nerves were basically classified into 2 types according to the cells which appeared and the characteristics of the lesions: Tumorous proliferation (T-type) and non tumorous response (R-type). Therefore, each case consisted of any of 3 types (T-type, T+R-type, R-type) (table 1).

TABLE 1 *Number of cases in each group according to the type of lesions*

TYPE OF LESIONS / GROUP	A	B	C	D	E	F	TOTAL
T	16	1	11	17	6	4	55
T+R	10	8	14	3	9	0	44
R	33	3	35	11	0	0	82
Total	59	12	60	31	15	4	181

a) T-type lesion

The lesions of this type were characterized by proliferation chiefly of cells of the lymphocytic series and partly of reticular or undifferentiated mesenchymal cells (tables 2 & 3). The distribution and degree of the lesions varied greatly between individuals, as did the sites of affected nerves. In mild lesions, the distribution of proliferative cells was comparatively sparse and perivascular cell accumulation was prominent. In moderate lesions, tumor cells showed infiltration between the neurites and their severe area often corresponded with macroscopic swelling of the nerves. In the more severe lesions, massive proliferation of tumor cells replaced almost completely the nerve tissues and furthermore, cell invasion extended penetrating through the perineurium to the surrounding tissues. These lesions were obviously neoplastic and some were found as macroscopically discrete

nodular tumors. In the nerves with heavy infiltration of lymphoid cells, damage of the neurites was often seen; demyelination, swelling or fragmentation of axons and appearance of scavenger cells were mentioned. These lesions were often difficult to find in the dense cellular area, but they were easy to find in the sparse peripheral area. Generally degeneration of nerve fibers was relatively slight, in spite of severe cell invasion. In severe case, marked Schwann cell proliferation and occasional participation of macrophages was also mentioned. Small patchy lesions of focal necrobiosis and the frame work of reticular fibers were occasionally observed in the dense cellular mass. In one of group C, a fibrin thrombus was markedly found in the lumbosacral plexus.

Furthermore, T-type lesions could be subdivided into 3 (T_I, T_{II}, T_{III}), according to the kind of cells which appeared. T_I-type lesions consisted of predominantly uniform small lymphoid cells. The size of these cells was that of mature lymphocytes, or a little larger. The nucleus was spherical and rich in chromatin. Irregular cytoplasmic processes were often seen (fig. 1). T_{II}-type lesions were commonly found. The cellular composition of lymphoid tumors of T_{II}-type consisted of pleomorphic cells which included small, medium and large lymphoid cells and fewer reticulum cells. The large lymphoid cells consisted of at least 2 kinds of cells; the one had a large distinct nucleolus and vesicular nucleus with basophilic cytoplasm and irregular cytoplasmic outline (hemocytoblastic), the other was smaller than the former and had a dark nucleus and cytoplasm (lymphoblastic) (fig. 15, 16 & 17). T_{III}-type lesions consisted of reticular or undifferentiated mesenchymal cells. These cells had relatively large pale nuclei and large nucleoli. Their cytoplasm was abundant and basophilic, and had irregular cytoplasmic processes. These cytoplasmic processes often connected with those of the adjacent cells. Mitosis and cell degeneration were frequent in each type of lesion (fig. 25).

b) R-type lesion

The lesions of this type were distributed loosely and sometimes sparsely in comparison with those of T-type. The lesions were characterized by diffuse infiltration of lymphocytes and plasma cells and accompanied by more or less edema (figs. 31, 32 & 33). The nerve fibers were separated and often accompanied by edematous fluids. Occasionally macrophages, fibroblasts and binucleated basophilic cells were found. On the other hand, perivascular focal cell accumulations which consisted chiefly of lymphocytes and partly of reticulum cells were also mentioned. Plasma cells were scarcely found. The degree of cell infiltration was usually mild or moderate, except in one case (tables 2 & 3). Proliferation of connective tissues was prominent between the neurites in some cases. In transverse section, the lesion had the appearance of a so-called "onion-bulb" structure (fig. 35). In more mild lesions, only a slight degree of lymphocytic infiltration or accumulation was present without gross nerve lesions. Demyelination was occasionally found in the edematous area.

c) Mixed T- and R-type lesions

The lesions of this type were found in about half the cases of the nerves with tumorous lesions. The lesions of both T- and R-types were present in the nerve fiber or in the different fibers in the same case. The lesions of T-type were usually at the roots and those of R-type were at the distal parts of the same nerves. Edema was not evident in

the T-type lesions, but edema and plasma cell infiltration were usually prominent in the R-type lesions. Swelling or fragmentation of axons, and demyelination were also found in the focal cell accumulation. Under LUXOL-fast-blue for myelin sheath staining, demyelination was more distinct coincidentally with focal cellular accumulation. In one of group C, fibrinoid swelling of the wall of the blood vessel was prominent in the brachial plexus (fig. 36).

Distribution of lesions Though the distribution and degree of lesions varied, tumorous proliferation (T-type) did not extend along the full length of the peripheral nerves. The lesions were particularly involved in the brachial plexus, lumbo-sacral plexus, ischiadic nerves, coeliac plexus (especially cranial mesenteric plexus) and vagosympathetic trunk, the degree of involvement being in this order. In the former two, the incidence of the lesions was usually high in the nerve roots or their dorsal root ganglia (fig. 28) and the degree of lesions tended to be severe. In the autonomic nerves in the various organs (fig. 17) and tissues (fig. 11), the distribution and degree of lesions also varied and 3 types of lesions (T, T+R, R) were found. Even in the grossly normal nerves, pathological changes were found under light microscopy. Focal and diffuse cell accumulations of lymphoid cells were observed in the interstitium of the spinal ganglia of the cervical, thoracal, lumbar and sacral parts (fig. 32). Though the degree of their lesions varied, in mild lesions, most of them consisted of R-type lesions. Edema and plasma cell infiltration were usually observed. In severe lesions, they showed a neoplastic nature (T-type). Though nerve cells in the ganglia were usually relatively intact, chromatolysis, vacuolization, atrophy and neuronophagia were occasionally seen.

In most cases, various degrees and stadium of degeneration and loss of nerve fibers, and edema were often found independently of cellular lesions (tables 2 & 3). Loss of nerve fibers was particularly found in the subperineurium. Edematous fluid, scavenger cells with vacuolated cytoplasm and networks of histiocytic cells were also observed (fig. 34).

Brain

Severe involvement of the brain was only seen in a few cases (table 2) (figs. 14, 18, 26 & 27). Massive cellular aggregations consisted chiefly of large lymphoid cells. The cells in the brain were usually similar to those invading the peripheral nerves. Affected areas were commonly found at the vicinity of the nerve roots (fig. 14), sometimes mid-brain and medulla oblongata. Some of the proliferative lesions were also found in the meninges and chorioid plexuses. Most of the proliferative lesions appeared perivascularly and they extended to the surrounding nerve tissues (fig. 27). Some of the lesions were associated with microglial proliferation and some astrocytes (table 2). Mitoses were frequent. On the other hand, perivascular cuffing was usually present in all parts of the brain (table 2) (fig. 30). It was mild or moderate and consisted chiefly of lymphocytes, adventitia cells and small pale nuclear cells. The cuffs consisted of various degrees of cell layer. Some were small consisting of only one to two layers of loosely arranged cells. The others were large consisting of several cell layers and cell invasion into the nerve tissues was marked. The distribution of the cuffs involving from one to two astrocytes surrounding the perivascular cuffs was also found and partly invaded the adjacent tissues (table 2). These astrocytes had homogeneously stained abundant cytoplasm and large pale nuclei.

TABLE 2 *Severity and incidence of nervous lesions in groups A, B and C (131 cases)*

LESIONS	NERVOUS TISSUES	SEVERITY OF LESIONS				INCIDENCE
		##	#	+	−	
						%
lymphoreticular *2 cell proliferation	peripheral	17	32	8	74	43.5
〃	central*1	1	8	0	61	12.9
cellular infiltration *3 (lymphocyte, plasma cell)	peripheral	1	29	71	30	77.1
perivascular cuffing	central*1	0	20	33	17	75.7
loss of nerve fibers and degeneration	peripheral	9	51	40	31	76.3
astrocytic proliferation	central*1	0	0	23	47	32.9

N. B.: *1 Examined only in 70 cases of groups A and B.
*2 T-type
*3 R-type
Lesions were graded on a (+) to (##) scale according to severity.
(##); severe, (#); moderate, (+); mild, (−); no lesions

TABLE 3 *Severity and incidence of nervous lesions in groups D, E and F (50 cases)*

LESIONS	NERVOUS TISSUES	SEVERITY OF LESIONS				INCIDENCE
		##	#	+	−	
						%
lymphoreticular *1 cell proliferation	peripheral	19	7	4	20	60
cellular infiltration *2 (lymphocyte, plasma cell)	〃	0	11	17	22	56
loss of nerve fibers and degeneration	〃	0	16	24	10	80

N. B.: *1 T-type
*2 R-type
Lesions were graded on a (+) to (##) scale according to severity.
(##); severe, (#); moderate, (+); mild, (−); no lesions

Some had a fibrous nature and focal astrocytosis was found in the central nervous system. Astrocytoma was found in one case with torticollis in group A.

Spinal cord

Focal cell accumulation was often found in the entrance of the nerve roots (fig. 19). The cells which composed it were similar to those invading the peripheral nerves. Focal cell accumulation seemed to be limited to the vicinity of small blood vessels and occurred frequently in the submeningeal area and the white matter. The cells extended often to

the nerve tissues and the nerve cells around the foci showed a slight degree of degeneration (atrophy). Some of the foci were associated with edema and slight reactive glia cell proliferation. Slight perivascular cuffing consisting of only a few lymphocytic layers was observed particularly in the nerve roots and the white matter (fig. 19).

Eye lesions

The optic nerve showed no remarkable changes, but the nerve fibers running through the eyeball revealed slight cell proliferation. Mitoses were also found. Proliferation of small, medium and large lymphoid cells was markedly observed in some parts of the ciliary body, sclera and chorioid membrane (fig. 13). Lymphoid cell proliferation was also found in the loose connective tissues around the eyeball. Infiltration of lymphocytes, plasma cells and heterophils was also observed in the chorioidea, iris, pecten and muscle tissues.

Visceral lesions

The severity of the lesions may be categorized in 3 grades according to the size and number of lymphoid foci, destruction of normal architecture, presence of mitoses and kinds of cells which appeared.

Mild (+): Microscopically the lesions involved 2 or 3 or several small lymphoid foci per section. The normal architecture was almost intact. These changes may be considered as an abnormal hyperplasia of the lymphoid tissues. The foci consisted chiefly of small lymphocytes and partly of reticulum cells.

Moderate (++): Microscopically the lesions consisted of tumorous proliferation of the lymphoid cells. The size and number of the foci definitely surpassed the former category, but their lesions were often fused into one. Destruction of normal architecture and mitoses were easily found. The cells were similar to those invading the peripheral nerves (T_I, T_{II}, T_{III}).

Severe (+++): Lymphoid tumors could easily be seen with the naked eye. Under light microscopy, the lesions were shown as a massive cell infiltation and were obviously neoplastic. The cells belonged to any of 3 types (T_I, T_{II}, T_{III}) (charts 1 & 2).

In comparison with the incidence of visceral lymphoid tumors in groups A, B & C and groups D, E & F, the latter showed a higher incidence than the former. The distribution of lymphoid tumors was shown as charts 1 & 2.

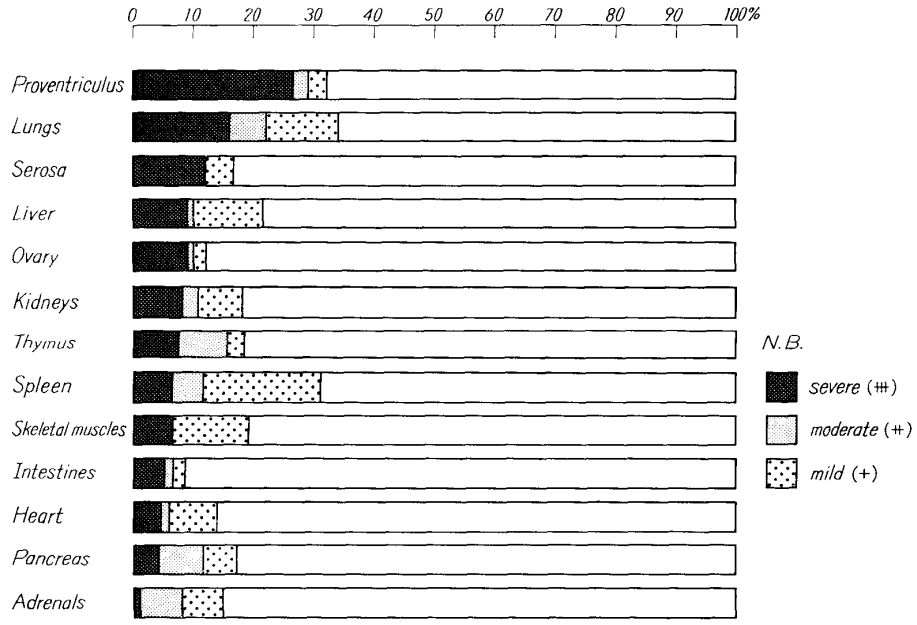
Liver

Focal cell accumulations were seen multiply in the interlobular connective tissues, especially around the small blood vessels. These foci were hyperplastic and spread by extension into the adjacent areas. They often fused into one and were observed in various sizes. The foci took the form of ill-defined nodular hyperplasia. Diffuse infiltration was partly seen in the sinusoids (T-type). The cells which appeared consisted mainly of those of T_{II}-type (fig. 21) and some were of T_I-(fig. 2) and T_{III}-types. In the lesions of T_{III}-type, fine networks of collagenous fibrils were also seen in the focal cell aggregations.

Spleen

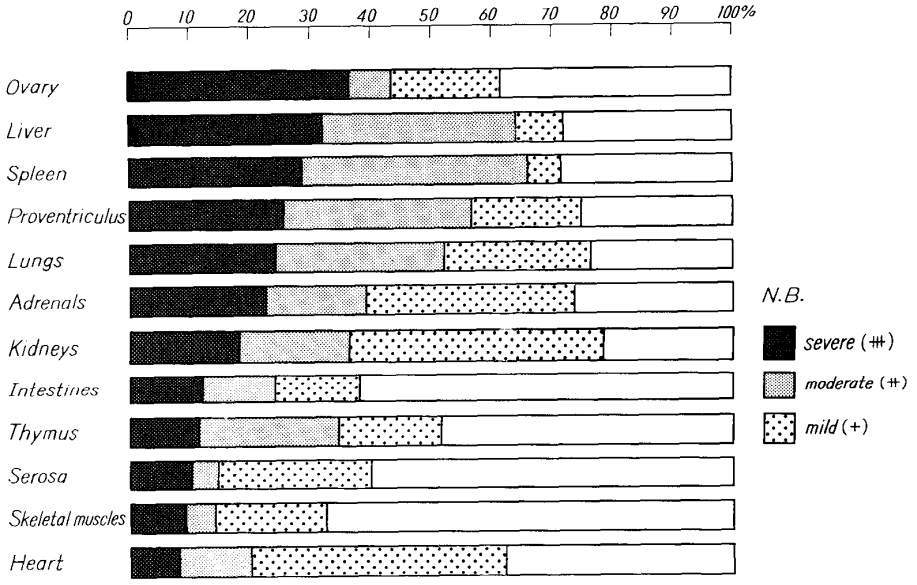
The proliferation of reticulum cells and lymphoid cells was markedly found around

CHART 1 *Distribution of visceral lymphoid lesions in groups A, B and C* (131 *cases*).



Lesions were graded on a (+) to (卅) scale according to severity.

CHART 2 *Distribution of visceral lymphoid lesions in groups D, E and F* (50 *cases*).



Lesions were graded on a (+) to (卅) scale according to severity.

the capillary sheath arteries (fig. 3). In some of the cases, the tumor cells proliferated in and over the fibrous capsule and spread to the subserosa. In the more severe cases, cell proliferation was more marked and the central part of the spleen was comletely replaced by tumor cells (T_I, T_{II}, T_{III}) (fig. 29).

Kidneys

Lympoid cell proliferation varying in extent was found between the tubules. In some, proliferation was so extreme that the parenchyma was completely replaced by tumor cells (T_I, T_{II}) (figs. 4 & 23) and only small parts of the parenchyma could be seen. Lymphoid cell infiltration was seen in and around the tunica propria of the ureter in almost every case.

Lungs

In the more severe cases, the lung parenchyma was also completely replaced by tumor cells except for the 3rd bronchioli (T_I, T_{II}). In some of these, the lungs were the seat of lymphoid growths in the form of diffuse or sporadic proliferation in the walls of the alveoli and around the 2nd or 3rd bronchioli (T_I, T_{II}). (fig. 6).

Heart

Larger areas of the myocardium were replaced by tumor cells in severe cases (T_I, T_{II}). Focal aggregations of tumor cells were usually observed in the loose connective tissues of the subepicardial area and the fat tissues around the coronary artery. In some cases, cell accumulations were found diffusely (fig. 5) or focally amongst the muscle fibers (T_I, T_{II}).

Ovary

In severe cases, the ovary was replaced by cauliflowerlike massive cell proliferation. Occasionally the anterior mesenteric plexus, coeliac plexus and periadrenal tissues in the vicinity of the ovary were invaded by tumor cells and consequently became ill-defined. The cells were similar to those invading the peripheral nerves (T_I, T_{II}, T_{III}) (figs. 9 & 10).

Adrenals

Focal cell accumulations were frequently observed in the interstitium of the peripheral area of the adrenals. Usually they consisted mainly of small lymphocytes. They were also small and few in number. In severe cases, tumor cell (T_I, T_{II}, T_{III}) proliferation was so marked that sometimes the parenchyma remained scattered in a few areas (fig. 7). The tumor cells invaded into the surrounding tissues and accordingly the coeliac plexus and nerve fibers were ill-defined.

Serosa

The tumor cells (T_I, T_{II}, T_{III}) proliferated nodulary or diffusely. Multiple tumor masses were also found macroscopically. The affected areas were mainly the subperitoneal tissues around the ovary, and the intestinal fat tissues.

Pancreas

In severe cases, a large focal proliferation of tumor cells was found in the pancreatic parenchyma and nerve fibers at the same time (T_I, T_{II}, T_{III}) (fig. 20).

Proventriculus

Marked tumor cell invasion was frequently observed in the muscularis mucosae, lobules

of glands, muscular layers and subserosa and consequently the mucous membrane and the glands thickened (T_I, T_{II}).

Gizzard

Slight cell infiltration was usually observed around the small blood vessels in the mucous membrane, muscle layers and subserosa.

Intestine

Marked tumor cell proliferation was often found in the tunica propria, muscle layers and subserosa and thickening of the intestinal walls was often marked in the small and large intestines (fig. 22). The lymphoid follicles in the mucous membranes of the caeca were hyperplastic and the boundary with adjacent tissues sometimes was unclearly demarcated.

Thymus

The thymus was often completely replaced by tumor cells in severe ceses (T_I, T_{II}) (fig. 8).

Bursa of Fabricius

Most of the lymphoid follicles were sharply demarcated and necrobiosis was frequently found in the center of the follicles. In some cases, the lymphoid follicles were unclearly demarcated and the surrounding tissues were replaced by a high degree of lymphoid cell proliferation (T_{II}).

Skeletal muscles

Perivascular focal cell aggregations (T_I, T_{II}, T_{III}) were often found and the foci extended into the surrounding tissues. In severe cases, wide areas of muscle tissue were replaced by these cells (figs. 12 & 24). At the same time, hyaline degeneration and reparative changes of the muscle fibers were frequently observed independently of these proliferative lesions. Muscular atrophy was occasionally found in cases of paralysis of a long duration.

Discussion

Peripheral nervous system

The pathological changes in the peripheral nerves in cases of Marek's disease have been reported by many workers, since the disease was first described by Marek in 1907. The early workers dealt with the disease as neuritis [Marek (1907), polyneuritis; Van der Walle & Winkler-Junius (1924), neuromyelitis gallinarum; Doyle (1926), neuritis; Dobberstein & Haupt (1927), polyneuritis interstitialis chronica]. On the other hand, Pappenheimer et al. (1929) attached more fundamental significance to the neoplastic nature as shown by lymphoid cell proliferation and they called the disease "neurolymphomatosis gallinarum." Furth (1935) further supported this concept and he regarded the inflammatory and degenerative changes as secondary to neoplastic proliferation. The nature

of the lesions in the peripheral nerves in Marek's disease has been a controversial subject for many years. One opinion regards the disease as inflammatory and the other regards it as neoplastic. In fact, both kinds of the lesion were often found in the nerves in Marek's disease. WIGHT classified the lesions of the peripheral nerves into the following 3 types. Type I was characterized by cellular infiltrations and relatively little edema. The majority of the infiltrating cells were small lymphocytes and plasma cells. Type II showed edema in contrast to type I, and the total number of infiltrating cells was small. In severe cases degeneration of the myelin sheaths and axons, and a tendency to fibrosis was marked. Type III was neoplastic and the lesions were characterized by a massive infiltration of morphologically similar lymphoblasts. PAYNE & BIGGS (1967) classified the lesions of the nerves in Marek's disease into 3 types, on the basis of their studies of the pathogenesis of Marek's disease. A-type was characterized by proliferation of the lymphoid cells, the presence of Marek's disease cells, and sometimes by demyelination and Schwann cell proliferation. B-type was characterized by diffuse infiltration by plasma cells and mainly small lymphocytes. Usually interneuritic edema, with occasional demyelination and Schwann cell proliferation was found. C-type lesion was characterized by light infiltration by plasma cells and small lymphocytes. They stated that the B-type lesion appears to be more inflammatory than the A-type, and the C-type lesion appears to be a mild form of the B-type.

In this report, the present authors could point out fundamentally the presence of two types of lesions in the peripheral nerves. One of the lesions was a tumorous proliferation (T-type) and the other was a non-tumorous response (R-type). The latter changes were considered as secondary reactive changes with an immunological basis, rather than inflammatory changes.

Although it was very difficult to draw a line between inflammatory, proliferative and neoplastic changes, changes which we described as lymphoid tumors are obviously neoplastic, because of the demonstration of systemic progressive proliferation, destruction of normal architecture, frequent mitoses, multi-focal or diffuse occurrences, and the occasional presence of cell abnormality. Furthermore, it might be said that the disease is closely connected with the nerve tissues. In the visceral lymphoid tumors, some might often be derived from the tumors of the autonomic neves in the visceral organs and tissues. Namely, lymphoid cells, in the autonomic nerves in the areas of the coeliac ganglia, adrenals, and periovarian tissues, proliferated passing through the perineurium into the adjoining tissues and made definite tumorous masses. A study of SEVOIAN & CHAMBERLAIN on experimental avian lymphomatosis due to JM agent suggested the idea of a primary neural change. They found evidence for a proliferation of neurolemmal

cells in addition to primitive mesenchymal cells, with differentiation to lymphoid cells. Their primitive mesenchymal cells may have some similarity to those of our T_{III}-type. In out T_I-type, the lesions consisted of uniform small lymphoid cells with the same characteristics in the peripheral nerves and visceral lymphoid tumors. In our T_{II} and T_{III} types, both lymphoid tumors in the peripheral nerves and visceral organs often consisted of cells with the same characteristics and cell groups. Both tumors were considered as the same kind of lesions of the same disease. Therefore the lesions of T-type in the peripheral nerves could adapt to the visceral tumors.

On the other hand, R-type lesions consisted of mature lymphocytes, plasma cells and fewer reticulum cells and were often accompanied by edema. We could not regard the R-type lesions as tumors from the characteristics of the lesions and we could not consider that the tumors arise from the differentiated cells. WIGHT suggested that the plasma cells may be of significance in the etiology of the disease in view of the relationship between the plasma cells and immunological reactions. PETEK & QUAGLIO (1967) demonstrated that experimental allergic neuritis was reproduced in chickens and lesions similar to WIGHT's types I and II occurred in the peripheral nerves. They considered that the analogy between the nervous lesions of the two diseases (allergic neuritis and Marek's disease) would support the hypothesis, first put forward by SILLER, that the degenerative and inflammatory nervous lesions of Marek's disease are due to autoimmune phenomena. HOWARD et al. (1967) revealed a significant increase in the level of 7S immunoglobulins which was found to coincide with the development of clinical signs and histopathologic lesions characteristic of the disease, 4 weeks after inoculation of Marek's disease agent. They considered that the alternative possibilities for the marked elevation of IgG levels in chicks infected with Marek's disease may be related to the development of a state of hyperimmunization or a secondary condition of autoimmunity due to the viral alteration of the proliferating lymphoid cells with resulting antibody production to cellular or foreign antigens. PAYNE & BIGGS supported a similar view with their B-type lesions. Furthermore, FOSTER & MOLL (1968) indicated that bursectomy or administration of large doses of cortisone acetate or 6-mercaptopurine altered the pathogenesis of Marek's disease in chickens. They assumed that the etiologic agent of Marek's disease is a neurotropic agent, and that the infection of peripheral nerves may cause alterations of antigenicity in neural tissues which might serve as antigens for initiating autoimmune reactions characterized by the peripheral nerve tissue destruction and monocytic cell infiltration. Therefore, an infectious agent may initiate the primary damage in the nervous tissues, but subsequent pathologic manifestations may have an immunologic basis. It is very

interesting that the above described facts, and the supporting hypothesis may give some suggestion of the pathogenesis of R-type lesions.

The most controversial subject is the interpretation of T+R-type lesions. This type was found in half of the cases having tumorous lesions. Since the lesions in the different bird varied quantitatively and qualitatively, the interpretation of lesions has been confused. The T-type in our cases may correspond with the A-type of PAYNE & BIGGS' cases and the R-type in our cases was similar to B- and C-types of their lesions. From the results of the experiment of the transmission of Marek's disease, PAYNE & BIGGS found that early in their experiment, the birds were most commonly associated with nerve lesions of the A-type and as time elapsed since infection, the nerve lesion followed the progression, A-type→mixed A- and B-type→B-type. They considered this process to be a regression of tumors. On the other hand, CAMPBELL[8] described that in fowl paralysis the early lesions consist of edema of the nerve followed by a chronic disease associated with inflammatory infiltrations in the nerves and viscera, and a progressive though not neoplastic accmulation of cells of the lymphoid series which eventually produce tumor-like lymphogranulomata. WIGHT[41] considered that a comparison of severely affected nerves from field cases of type I with those of type III seems to indicate a gradation between inflammatory reactions and frank neoplasia. On the other hand, YAMAGIWA et al. (1967) described that the cells which they term light and dark cells are considered to be due to abnormal hyperplasia of the lymphatic tissue—perhaps better described more generally as mesenchymal tissue—, which pervades the whole body and both types of cells, from the light to the dark cells. As we stated above, opinions about the pathogenesis of the disease differed according to the author; some supported the process of T→R, whereas the others the process of R→T. In consideration of the possibility of a close relationship between the R-type lesions and an immunological phenomena, and the results of a study of experimental transmission by PAYNE & BIGGS, it may be suggested that the process from T to R types might exist or that the R-type might continue from beginning to end. From the characteristics of the lesions, the T-type lesions were often found in the fatal and acute cases, whereas R-type lesions were frequently found in the chronic cases. T+R-type lesions also mediated between both T- and R-types. On the pathogenesis of the disease, though it is interesting, we need more study, because our materials consisted only of field cases.

On the degenerative changes in the peripheral nerves of Marek's disease, JUNGHERR & HUGHS described that the lesions may be associated with edema, myelin degeneration, and reactive increase of Schwann cells, but axonal degeneration is rare. WIGHT[41] demonstrated edema, degeneration of myelin sheaths

and axons, proliferation and increase of Schwann cells, remyelination and formation of Büngner's bands. He also indicated extensive edema combined with interstitial fibrosis, particularly lamellae of the connective tissu forming an "onion bulb." PAYNE & BIGGS observed a fine reticular network in the cell masses and the edematous spaces sometimes contained a light eosinophilic network which appeared to consist of protein material with occasional reticulin and collagen fibers. In the present cases, though we found lesions similar to Wallerian degeneration corresponding to cell proliferated foci, degeneration and loss of nerve fibers with more or less edema was often found independently of cell infiltration or proliferated foci. Such lesions were frequently observed in the peripheral nerves of other domestic animals as polyneuropathy[20,35,36,37]. Therefore we considered that the lesions were different from those of Marek's disease.

Central nervous system

Perivascular infiltration made up predominantly of small lymphocytes was found in the central nervous system in mild or moderate grades (75.7%) (table 2). PAPPENHEIMER et al. (1929), McGAUGHEY & DOWNIE (1930), LERCHE & FRITZSCHE (1934) and many other workers mentioned that no involvement of lesions of the central nervous system was found in a few cases of the disease. Therefore, the lesions are not constantly present in the central nervous system of birds affected with Marek's disease. Though FINDLAY & WRIGHT (1933) did not find perivascular cuffing in equal proportions in healthy birds in flocks both affected with and free from fowl paralysis. JUNGHERR (1935) found it in 38% of the control cases. WIGHT (1962)[42] grouped perivascular infiltrations into 6 grades according to their severity and he described that too much significance should not be attached to these vascular lesions when they occur because in only 7% of the cases of fowl paralysis was the degree of cuffing more severe than observed in some clinically unaffected control birds. He also revealed a few astrocytes surrounding the moderately large perivascular cuffs. The processes of these astrocytes were often enlarged, thickened and layered around the cuff. It suggested a chronic and regressive process. Usually primary neural or myelin changes were not observed. Secondary changes were infrequent and usually resulted from severe infiltration or mechanical distortion of the central nervous system. In the cases at present under investigation, tumorous proliferation of the lymphoid cells was observed with marked parenchymatous degeneration in a few cases. The cells which appeared consisted mainly of lymphoblastic or immature cells of the lymphoid series with large pale nuclei. These cells were similar to those seen in the lymphoid lesions of the peripheral nerves (T_{II}). Reticular or undifferentiated mesenchymal cells similar to those found in the peripheral nerves were

observed around the blood vessels in the central nervous system (T_{III}). Cell proliferation was also found in the meninges and chorioid plexus. Mitoses of tumor cells were frequently seen and tumorous proliferation was observed in the entrance of the nerve roots and the other parts of the brain. Perivascular infiltrations and astrocyte proliferation around the vessels were often found. The latter process was often chronic. It may have some connection with changes which ITAKURA et al. described as "encephalonecrobiosis disseminata of chickens." Focal encephalomalacia were found in 2 cases examined. Astrocytoma was also found in 2 other cases. It is interesting that there was proliferation of astrocytes around the area of the astrocytoma. The proliferation of astrocytes itself was considered to have no connection with the characteristic features of Marek's disease.

Eye lesions

It is already known that there is abnormality of the eyes, distortion of the pupils, loss of normal pigments and iritis in cases of acute or classical Marek's disease. The present authors also pointed out similar change in the eyes of our cases. T-type lesions in the eyes were considered obviously to be one part of the systemic lymphoid tumors which occurred in the whole body. Some of the cases showed marked plasma cell reaction.

Visceral lesions

As visceral lesions, tumorous proliferative lesions similar to those seen in the peripheral nerves could be pointed out in the visceral organs and tissues (T_I, T_{II}, T_{III}). The cells made up visceral tumors have usually been called lymphoid cells or mononuclear cells. PAYNE & BIGGS stated that the ovarian tumors were composed of a diffusely proliferating mixture of blast cells, medium and small lymphocytes, Marek's disease cells, and activated and primitive reticular cells. Plasma cells were not found. Cytologically the lymphomatous process appeared to be identical to that in the nerve with A-type lesion. They also stated that the composition of lymphoid tumors occurring in the other organs was similar to that of the ovarian tumors, although the gross pattern of involvement varied from areas of diffuse infiltration to discrete nodular tumors. BANKOWSKI et al. (1969) described that most of the tumor cells seemed to be prolymphocytes; a few lymphoblasts and reticular cells were found in Giemsa-stained impression smears. YAMAMOTO et al. (1967) classified the visceral lesions of Marek's disease into the following 3 categories to the histological characteristics: i) lymphogranulomatous lesions, ii) reticulosarcoma-like or lymphosarcoma-like lesions, iii) lymphoblastoid lesions. SEVOIAN & CHAMBERLAIN (1964)

concluded that the lesions mainly consisted of proliferated cells originating from the primitive mesenchymal cells of the tunica adventitia of the arterioles, neurilemmal cells and the lining cells of the hepatic sinusoids, in descending order of incidence.

In the present cases, cell proliferation was markedely seen in the interlobular connective tissues, especially around the small blood vessels in the liver. In the spleen, proliferation was seen around the capillary sheathed arteries. In the ovary, adrenals and kidneys, etc., proliferation started around the capillary or small arterioles in various tissues and extended into the adjoining tissues. In severe cases, proliferation had become so massive as to suggest a distinct neoplasm (charts 1 & 2). From the above findings, it may be considered that tumor cells may originate from lymphoreticular tissues around the blood vessels. Namely, it may be appropriate to consider that tumorous lesions consisted of proliferated tumor cells which may come from lymphoreticular cell originating from the extracapillary reticular tissue, that is the undifferentiated primitive mesenchymal tissues in the whole body.

Both groups A, B & C (classical Marek's disease) and groups D, E & F (acute Marek's disease) had fundamentally no pathological differences, except for the variation of clinical findings, epidemiology and incidence of visceral tumors. As both the diseases had T-, T+R- and R-types of lesions, all investigated cases may be regarded as the same disease. All our cases were similar to those of "neurolymphomatosis gallinarum" which was described by PAPPENHEIMER et al.[31,32], from the pathological characteristics and were categorized as "Marek's disease" as proposed by BIGGS[4].

Classification of classical and acute forms of Marek's disease has been largely due to epidemiological convenience. Accordingly, this classification is not always appropriate for pathology.

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EXPLANATION OF PLATES

PLATE I

Fig. 1 Proliferation of uniform small lymphoid cells between the neurites and axonal swelling are prominent TI-type plexus brachialis E 5391 H. & E. × 190

Fig. 2 Proliferated foci of small lymphoid cells in the liver TI-type E 5391 H. & E. × 120

Fig. 3 Proliferation of uniform small lymphoid cells around the sheathed arteries in the spleen E 5391 TI-type H. & E. × 190

Fig. 4 Focal small lymphoid cell accumulation in the kidney E 5391 TI-type H. & E. × 49

Fig. 5 Diffuse proliferation of small lymphoid cells in the intermuscular fibers of the heart E 5391 TI-type H. & E. × 190

Fig. 6 Lymphoid tumor around the tertiary bronchi of the lung E 5526 TI-type H. & E. × 48

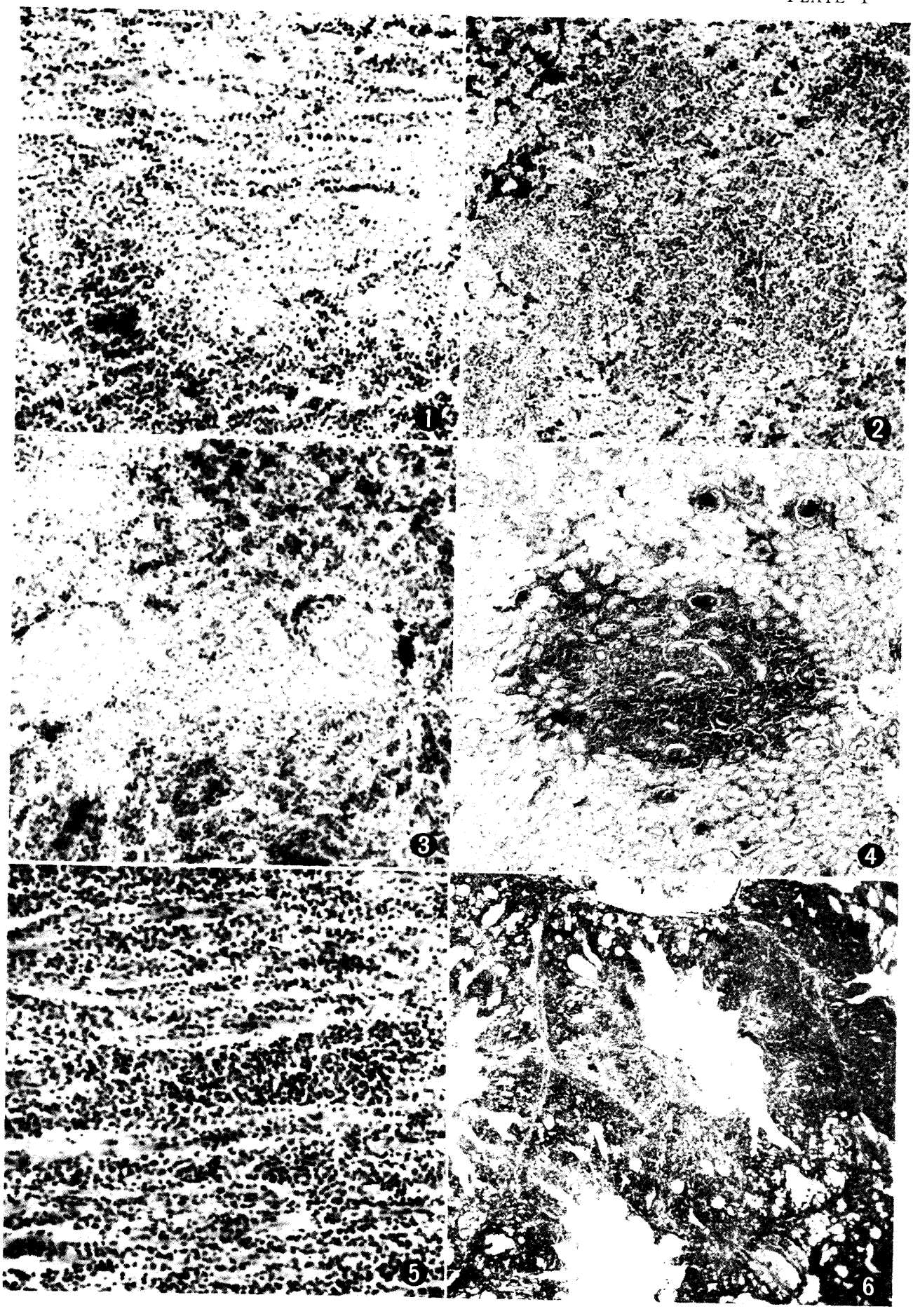
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PLATE II

Fig. 7 Massive small lymphoid cell invasion in the adrenal E 5391 T_I-type H. & E. × 49

Fig. 8 Diffuse small lymphoid cell proliferation in the thymus E 5491 T_I-type H. & E. × 378

Fig. 9 Small lymphoid cell proliferation in the ovary E 4446 T_I-type H. & E. × 131

Fig. 10 Higher magnification of fig. 9 Lesions consisted of uniform small lymphoid cells ovary E 4446 T_I-type H. & E. × 1300

Fig. 11 Small lymphoid cell invasion in the area of the soft palate. Infiltration of the same kind of lymphoid cell is seen in the intervening nerve fibers E 4446 T_I-type H. & E. × 131

Fig. 12 Small lymphoid cell invasion intermuscular fibers in the M. gastrocnemius E 5526 T_I-type H. & E. × 190

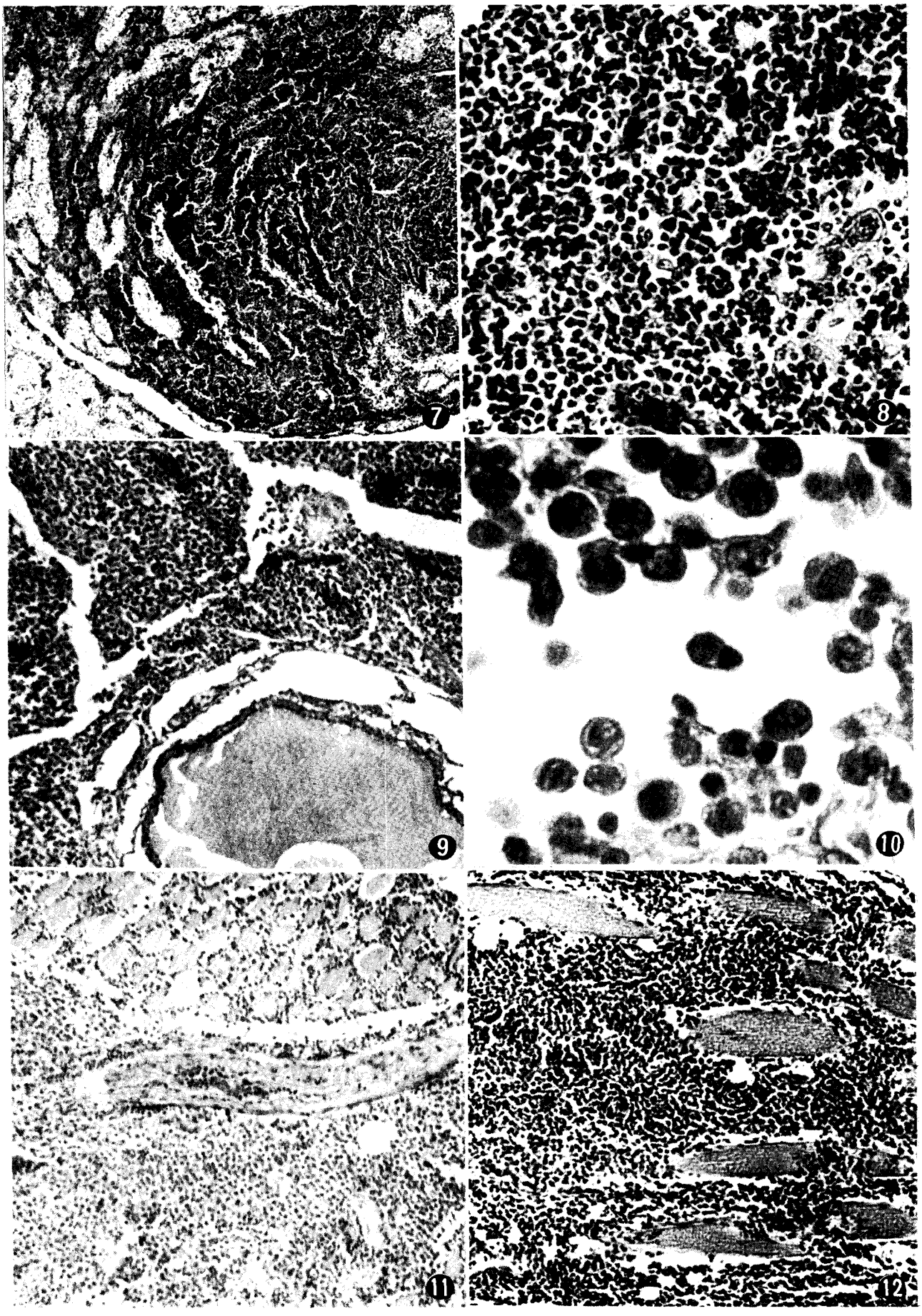


PLATE III

Fig. 13 Small lymphoid cell proliferation in the chorioidea of the eye E 4446 T_I-type H. & E. × 121

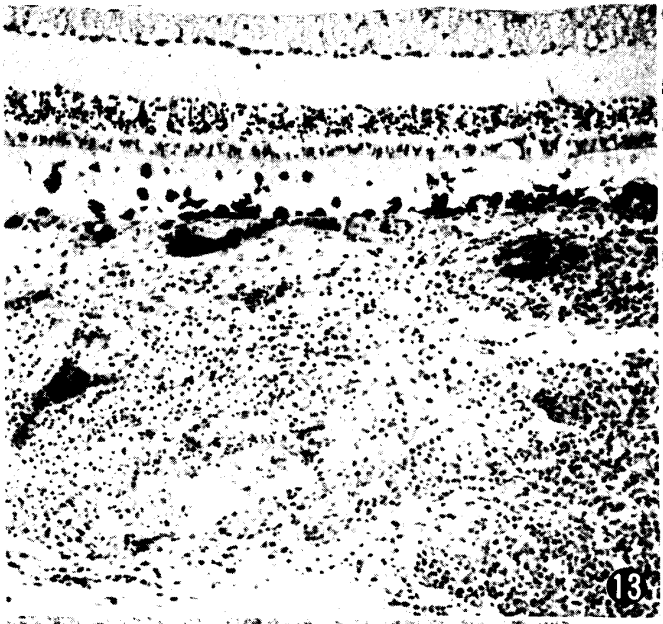
Fig. 14 Small lymphoid cell invasion in the nerve root of the brain E 4446 T_I-type × 81

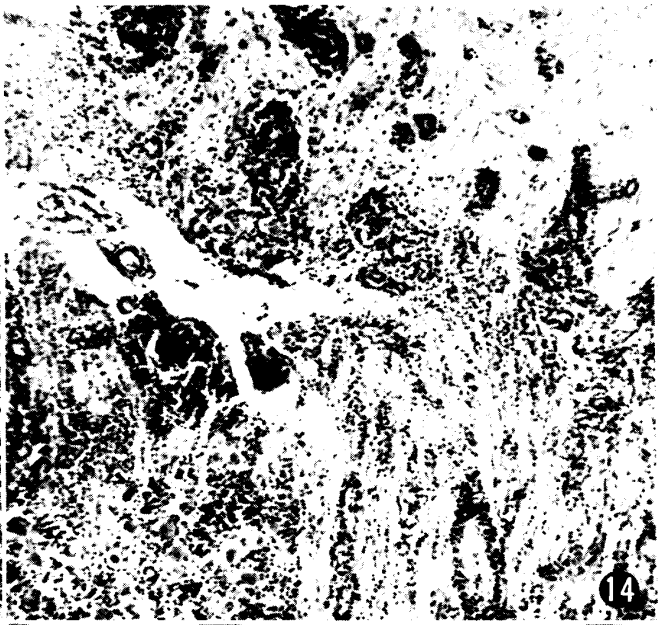
Fig. 15 Severe T_{II}-type nerve lesion, showing lymphoid proliferation between the neurites and especially perivascular accumulations are evident N. tibialis E 4240 H. & E. × 81

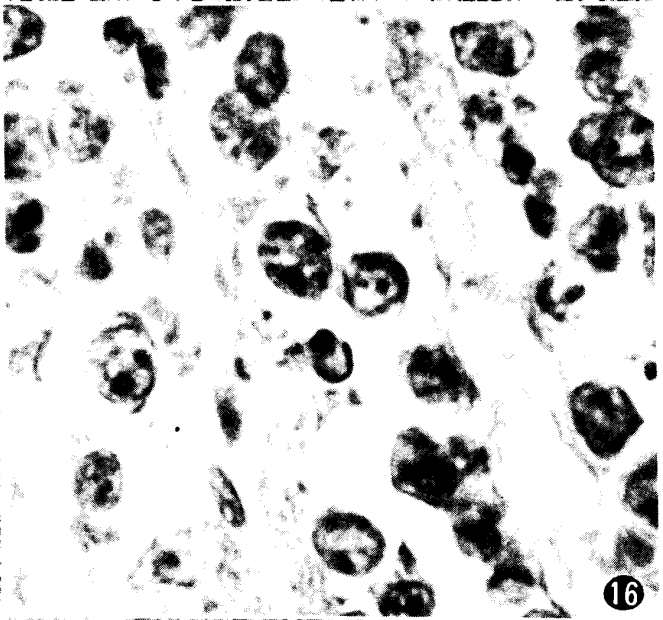
Fig. 16 Small, medium and large lymphoid cells and fewer reticulum cells in the T_{II}-type nerve lesion plexus lumbosacralis E 4370 H. & E. × 1300

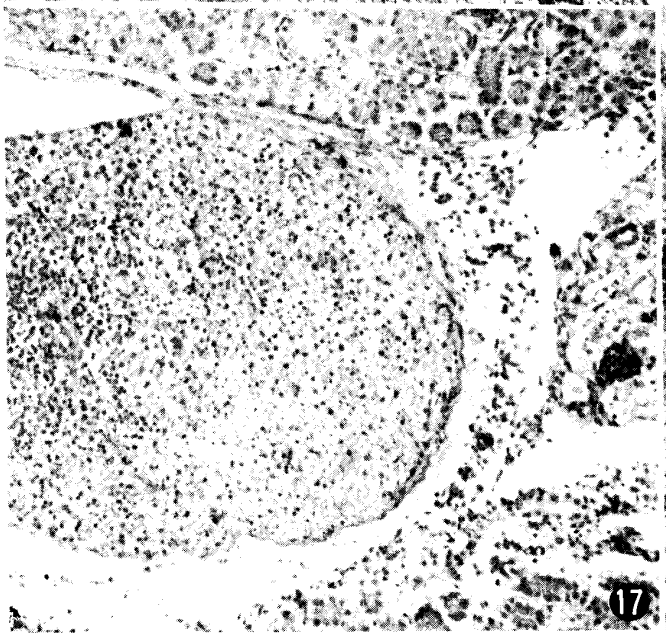
Fig. 17 Infiltration of lymphoid cells in the intervening nerve fiber of the kidney E 4240 T_{II}-type H. & E. × 131

Fig. 18 Lymphoid cell invasion in the vicinity of the nerve root of the brain E 4342 T_{II}-type H. & E. × 81









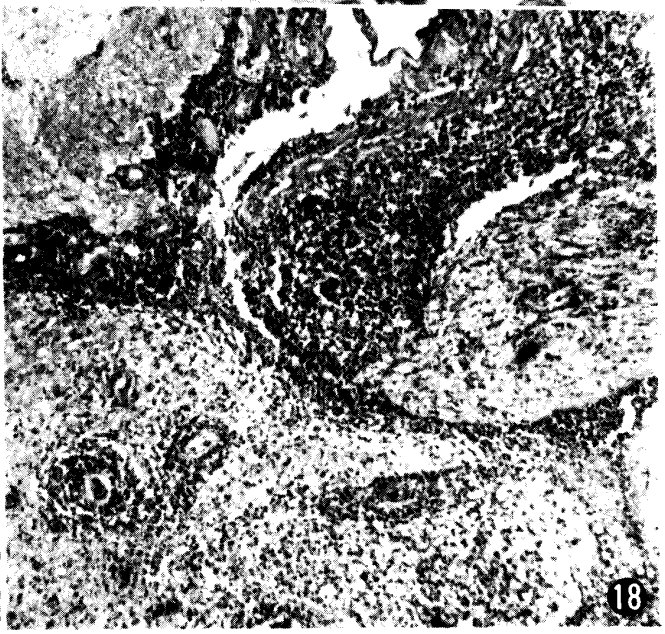


PLATE IV

Fig. 19 Lymphoid cell invasion in the vicinity of the entrance of the nerve root, submeningeal area and the white matter of the spinal cord E 4370 T_{II}-type H. & E. × 77

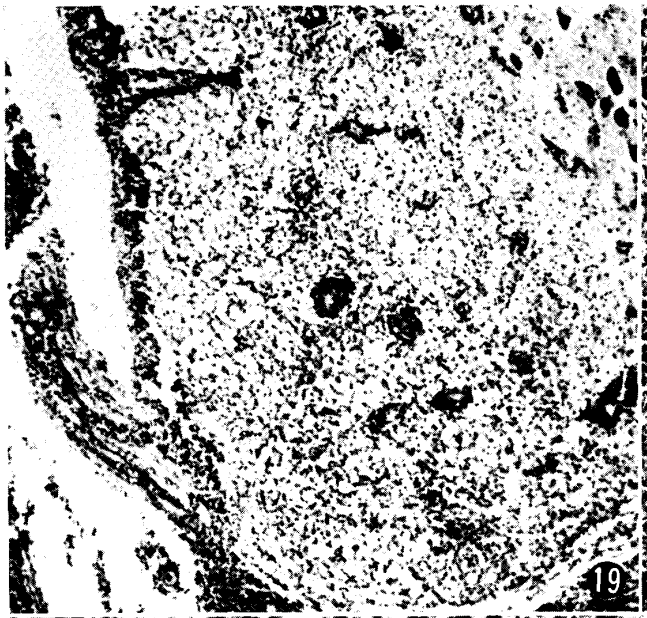
Fig. 20 Lymphoid cell proliferation in the intervening nerve fibers and the parenchyma of the pancreas E 4370 T_{II}-type H. & E. × 81

Fig. 21 Lymphoid foci of the liver E 5431 T_{II}-type H. & E. × 378

Fig. 22 Massive proliferation of lymphoid cells in the large intestine E 5528 T_{II}-type H. & E. × 120

Fig. 23 Proliferation of lymphoid cells in the kidney E 5443 T_{II}-type H. & E. × 750

Fig. 24 Lymphoid cell proliferation in the intermuscular fibers of the skeletal muscle E 5528 T_{II}-type H. & E. × 190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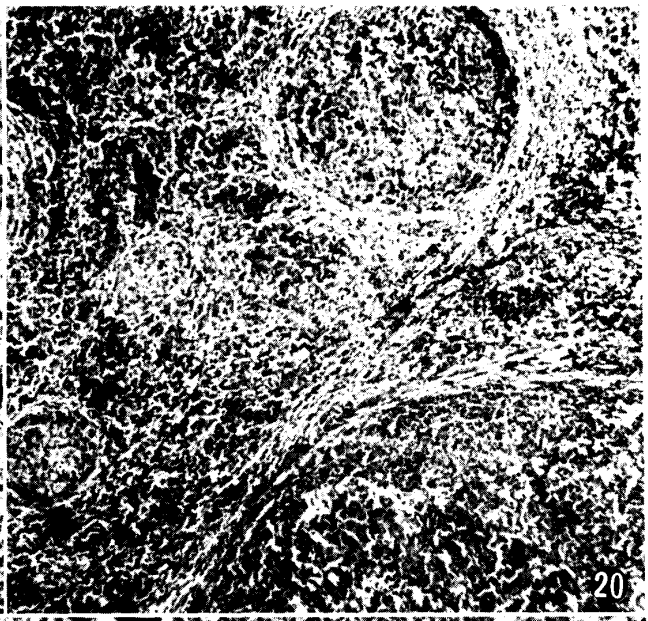
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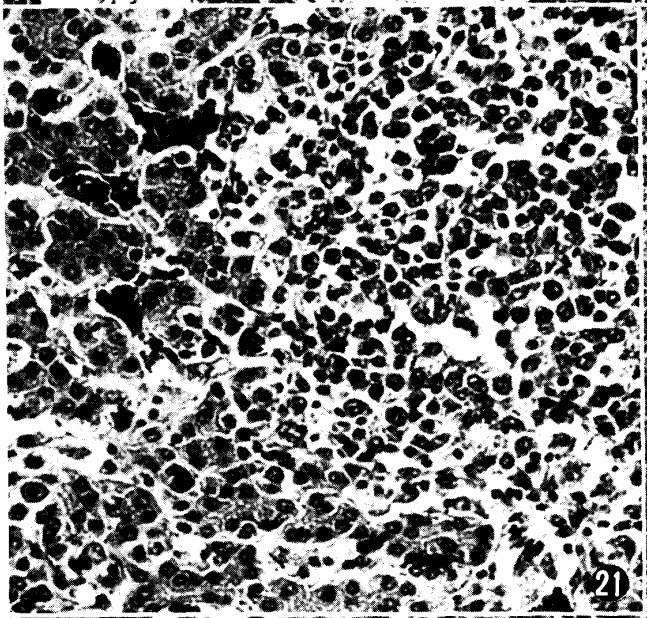
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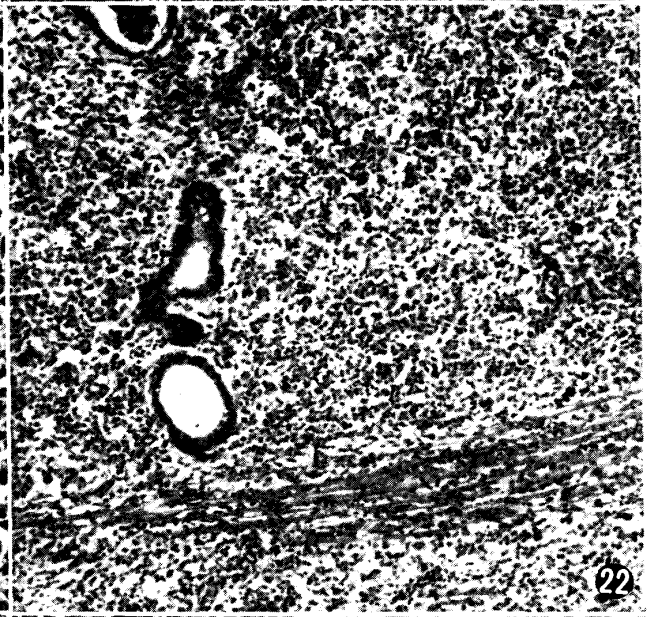
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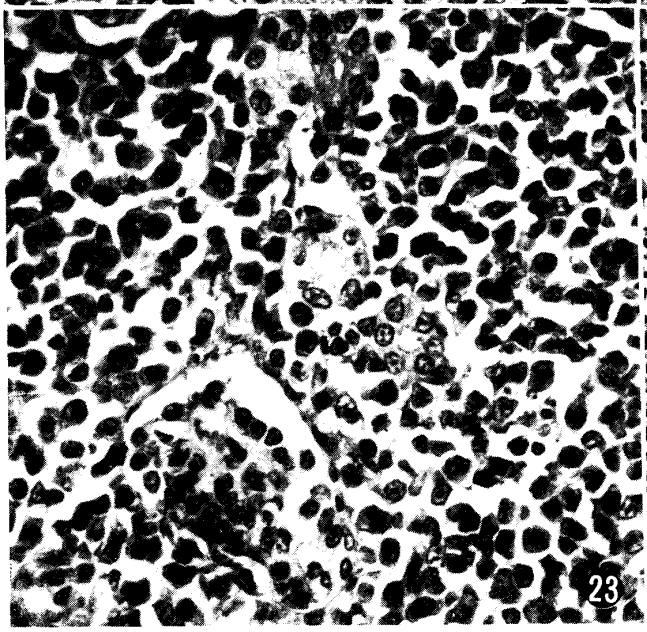
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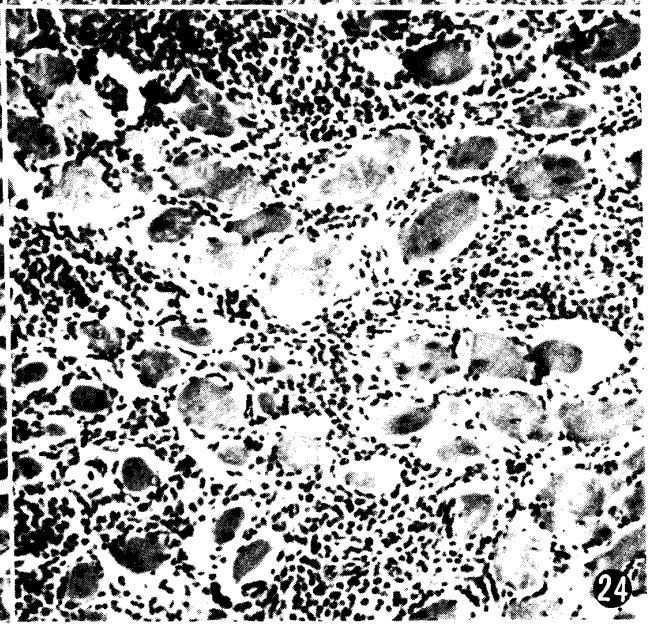
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PLATE V

Fig. 25 Reticular or undifferentiated mesenchymal cell proliferation (T_{III}-type) between the neurites of N. vagus E 4371 H. & E. × 495

Fig. 26 Perivascular cell proliferation in the meninges E 4372 T_{III}-type brain H. & E. × 325

Fig. 27 Proliferation of T_{III}-type cells in the brain E 4372 H. & E. × 81

Fig. 28 Proliferation of T_{III}-type cells in the spinal ganglion E 4372 H. & E. × 495

Fig. 29 Perivascular proliferation of T_{III}-type cells in the spleen E 3256 H. & E. × 515

Fig. 30 Perivascular cuffing in the brain E 4184 H. & E. × 515

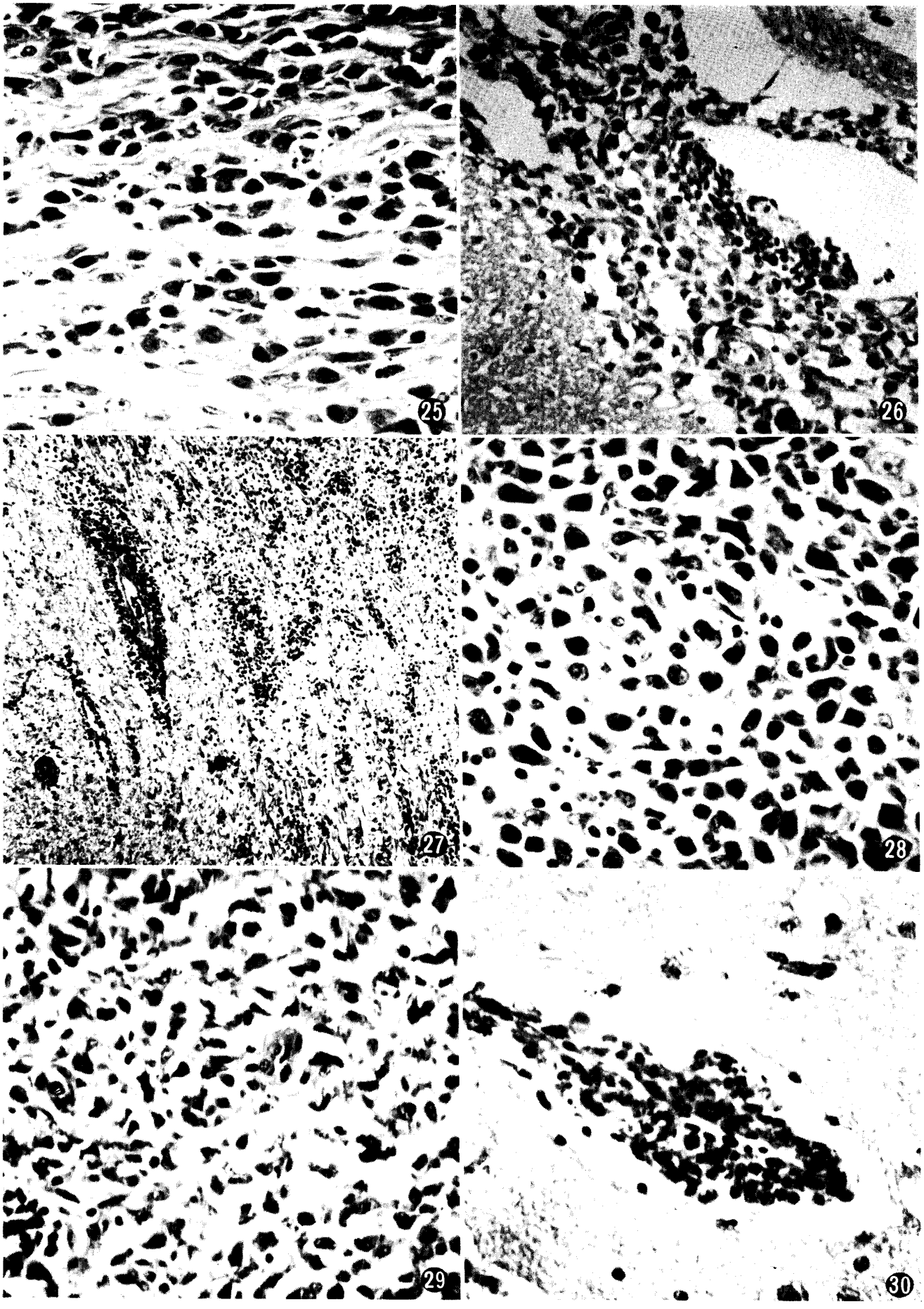
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PLATE VI

Fig. 31 Infiltration of small lymphocytes and plasma cells between the neurites. Moderate interneurite edema and early demyelination and loss of nerve fibers E 4598 N. tibialis R-type H. & E. × 131

Fig. 32 Perivascular accumulation and infiltration of small lymphocytes and plasma cells with edema and nerve degeneration in the nerve root of the spinal cord E 4507 R-type H. & E. × 81

Fig. 33 Infiltration of small lymphocytes and plasma cells with edema. Activated Schwann cells with round or oval nuclei are present E 4231 plexus lumbosacralis R-type H. & E. × 750

Fig. 34 Degeneration and loss of nerve fibers with edema in the subperineurium E 4425 plexus brachialis R-type H. & E. × 81

Fig. 35 Perineurite connective tissue forming the so-called "onion bulb" structure in transverse section of the plexus brachialis E 4425 R-type H. & E. × 515

Fig. 36 Fibrinoid swelling of the wall of a blood vessel in the plexus brachialis E 5355 R-type H. & E. × 378