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PATHOLOGICAL STUDIES ON SO-CALLED "KIRIYOI DISEASE"

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INTRODUCTION

From many years ago, there has been a disease of unknown cause, known as so-called "Kiriyo disease", in Japanese cattle in mountainous grazing areas of Chugoku district, mainly in Tottori, Shimane, Hiroshima and Okayama Prefectures in Japan. Up to date, no comprehensive pathological study has ever been made on this disease. The authors, therefore, suspect that there is no proper interpretation in this regard other than opinions based on a unilateral or vague conceptions.

As a part of studies on "Kiriyo disease", the authors have conducted comprehensive pathological studies on Japanese cattle which were regarded by owners as suffering from "Kiriyo disease" and collected mainly by the staff members of the Kiriyo Disease Research Team of Tottori University.

The investigation made it possible for the authors to prove definitely the degeneration and the loss of granule cells, as a new outcome which no one could previously even think of, in nearly the whole area of the granular layer in the cerebellar cortex in all cases subjected to the investigation of the central nervous system excepting one case. In this connection a detailed report has already been made under the theme of "Cortical Cerebellar Atrophy of Granular Type in Japanese Cattle" by YAMAGIWA and certain of the present authors²³⁾.

The authors, at this time, conducted investigation principally on visceral changes of so-called "Kiriyo disease", and also conducted simultaneously comprehensive pathological studies on the problem of what role cerebellar changes had played in the said disease.

In order to clarify the character of the disease, the authors have decided

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to analyze it boldly without regard to incomplete materials for investigation as such cases were regarded alone by the owners as "Kiryoi disease." It is hoped that the summarized findings based on the patho-morphological point of view will be of assistance to the investigation of the disease in the future. The authors would appreciate any comment on this report.

MATERIALS AND METHODS

Materials investigated, as shown in the following table, consist of 15 mortal cases and 1 slaughtered case of young cattle regarded as having suffered "Kiryoi disease" by the owners in Hino-gun, Tottori Prefecture where the disease is normally found. The materials were collected during the period from 1951 and 1958 inclusive. Of these materials, study was made on the central nervous system of 12 cases, on which a detailed report has already been presented by Prof. YAMAGIWA and others.

TABLE. *List of Materials Investigated*

CASE NO.	PROTOCOL NO.	SEX	AGE	DATE OF AUTOPSY	TERMINATION	LOCALITY
1*	176	?	?	'51	†	Hino-gun, Hinogami-mura
2*	177	"	"	'52	"	" "
3*	288	"	"	7/V '53	"	" Fukuei-mura
4	289	"	"	11/VII '53	"	" "
5	353	♂	2j	24/VI '53	"	" Iwai-mura
6*	354	"	11m	2/VI '54	"	" Hinogami-mura
7	438	"	?	13/VI '55	"	" Fukuei-mura
8	483	"	7m	12/V '56	"	" Hakunami-mura
9	488	♀	11m	14/VI '56	‡	" Tari-mura
10	571	♂	15m	24/V '57	†	" Hakunami-mura
11	573	"	13m	4/VI '57	"	" Tari-mura
12	582	"	15m	21/VI '57	"	" "
13	643	"	12m	17/V '58	"	" Takamiya-mura
14	649	"	9m	23/V '58	"	" Tari-mura
15	650	"	15m	26/V '58	"	" Takamiya-mura
16	651	"	12m	26/V '58	"	" "

* Astrisk indicates the cases which did not provide materials from the central nervous system.

The majority of such animals were found in pasture as carcasses. The course of the disease, however, was estimated to be one-half day to two and a half days since some of cases were obtained while animals were still alive. In consequence, there was no way to obtain clinical data from their lifetime. The authors understand that cases of living

animals which have been obtained showed typical symptoms of the disease. Autopsy was conducted approximately 15 or 30 hours after the death of the animals on an average due to the delay in discovering and reporting as a result from geographical conditions except one slaughtered case (No. 9) and case No. 6 obtained 4 days after death.

Except 6 cases which were sent to the writers for examination (Nos. 1~6), all the cases were autopsied by GOTO and others at the site. The materials obtained from each organ were fixed with 10% formalin after being observed macroscopically. Most of the materials were embedded with paraffin and stained with hematoxylin-eosin, but celloidin embedding and cresyl violet staining were employed on some parts of the cerebellum and posterior parts of the brain stem tissue. Spielmeyer's myelin sheath stain, Bielschowsky's impregnation method and Sudan III stain by frozen sections were applied.

RESULTS OF OBSERVATIONS

Pathological-Anatomical Changes

No. 1~No. 6...Details were not obtainable as materials were sent from a distance for examination.

- No. 7...1) Acute catarrhal laryngo-tracheitis and bronchitis
- 2) Acute passive hyperemia of the spleen
- 3) Dilatation of the right heart ventricle
- 4) Swelling of the liver
- 5) Passive hyperemia of the kidneys
- 6) *Setaria digitata* in the peritoneal cavity
- No. 8...1) Congestive edema of the lungs
- 2) Acute passive hyperemia of the spleen
- 3) Dilatation of the right heart ventricle and edema of the bicuspid valve
- 4) Congestive edema of the epiglottis
- 5) Acute passive hyperemia of the kidneys
- 6) Cloudy swelling of the liver
- 7) Hyperemia and catarrhal inflammation of the stomach, ileum and coecum
- No. 9...1) Killed (general anemia)
- 2) Congestive edema of the left lung and alveolar emphysema of the right lung
- 3) Acute passive hyperemia of the spleen
- 4) Petechiae in the subendocardium
- 5) Catarrhal enteritis with accompanying abscesses
- 6) White spots in the cortex of the kidneys
- 7) Passive hyperemia of the liver and gall stagnation
- 8) Intraorbital abscess
- No. 10...1) Congestive edema of the lungs
- 2) Acute passive hyperemia of the spleen
- 3) Hydrothorax and ascites
- 4) Interlobular edema of the thymus

- 5) Icterus of the liver
 - 6) Passive hyperemia of the kidneys
 - 7) General anemia
 - 8) Catarrhal and hemorrhagic gastro-enteritis
 - 9) *Paramphistomum cervi* in the reticulum
- No. 11...1) Acute passive hyperemia of the spleen
- 2) Petechiae of the subendocardium and dilatation of the heart ventricles
 - 3) Passive hyperemia of the lungs and kidneys
 - 4) General anemia
 - 5) *Setaria digitata* in the peritoneal cavity, *Oesophagostomum* sp. in the colon and *Haemaphysalis* sp. on the skin
- No. 12...1) Catarrhal broncho-pneumonia
- 2) Swelling of the *Lnn. mesenterici*
 - 3) Severe cloudy swelling of the liver and kidneys
 - 4) Acute swelling of the spleen
 - 5) Dilatation of both ventricles of the heart
 - 6) Interlobular edema and congestion of the thymus
 - 7) Catarrhal gastro-enteritis
 - 8) *Setaria digitata* in the peritoneal cavity
- No. 13...1) Congestive edema of the lungs
- 2) Acute passive hyperemia of the spleen
 - 3) Dilatation of both ventricles of the heart
 - 4) Acute passive hyperemia of the kidneys
 - 5) Swelling of the lymph nodes
 - 6) Cloudy swelling of the liver
 - 7) Catarrhal gastro-enteritis, with petechiae in the small intestines
 - 8) Congestion of the blood vessels in the meninges of the brain
 - 9) *Setaria digitata* in the peritoneal cavity
- No. 14...1) Congestive edema of the lungs and larynx
- 2) Acute passive hyperemia of the spleen
 - 3) Dilatation of the right heart ventricle
 - 4) Swelling of the general lymph nodes
 - 5) Passive hyperemia of the kidneys
 - 6) Necrotic spots in the liver
 - 7) Catarrhal gastro-enteritis and nodular formation of rice grain size in the ileum and coecum
- No. 15...1) Congestive edema of the lungs
- 2) Acute passive hyperemia of the spleen
 - 3) Dilatation of both ventricles of the heart
 - 4) Passive hyperemia of the kidneys
 - 5) Cloudy swelling of the liver
 - 6) Catarrhal gastro-enteritis
 - 7) Sugillatio of the subcutaneous tissue of the fore breast

- 8) *Bunostomum phlebotomum* in the duodenum
- No. 16...1) Acute catarrhal broncho-pneumonia
- 2) Necrotic spots in the liver
- 3) Acute passive hyperemia of the spleen
- 4) Dilatation of the right heart ventricle
- 5) Acute passive hyperemia of the kidneys
- 6) Catarrhal gastro-enteritis and ecchymosis of the abomasum
- 7) Acute catarrhal cystitis
- 8) Sugillatio of the subcutaneous tissue of the *Articuli tarsi*
- 9) *Setaria digitata* in the peritoneal cavity

Histopathological Findings

Liver: *V. centralis* and sinusoids were severely dilated. Generally accompanied either by congestion or congestive edema. Dilatation and edema of Disse's spaces were present in many cases. Some showed the congestion predominantly in the peripheral lobules (Nos. 9, 11, 12 & 14) or central lobules (Nos. 10 & 13). Reticulo-endothelial cells of intraacinous sinusoids generally showed a slightly activation. The arrangement of intraacinous liver cell cords was generally well maintained but the dissociation of liver cells and the atrophy of centroacinous liver cell cords were sometimes noted. Often cytoplasm of liver cells contained small vacuoles. Small or large nodules were often observed as associated lesions. Nodules were composed mainly of histiocytic cells and lymphocytes, the former of which often accumulated as naked nuclei. There were nodular lesions with coagulative necrosis in their central portion, accompanied by the accumulation of histiocytic cells and lymphocytes in their marginal portion (Fig. 11). Other lesions observed were necrobiotic and necrotic foci accompanied by reactively formed swollen naked nuclei. Emigration of polymorphonuclear and eosinophil leucocytes was often seen in the intraacinous sinusoids, and some showed many fibrin thrombi in the blood vessels (No. 2). Glisson's sheath sometimes exhibited fibrinoid swelling of the walls of the arterioles (No. 5).

Spleen: Generally exhibited acute passive hyperemia; splenic pulp was rich in blood content showing like a "Blutmeer." Splenic sinus was severely dilated and sometimes accompanied by hemorrhages in the splenic trabeculae and Malpighian bodies. The Malpighian bodies were generally poor in cells and were pale and edematous. There were various cases which showed enlargement and hyperplasia in Malpighian bodies as in No. 9, activated reticulum cells in Malpighian bodies sometimes accompanied by mitosis and scattering pigment phagocytes (No. 11), formation of necrobiotic foci and proliferation of reticulum cells in Malpighian bodies (No. 7), fibrinoid swelling of the walls of the central arterioles in the Malpighian bodies (No. 14), and fibrin thrombi in the splenic sinus (Nos. 2 & 10).

Kidneys: Showed severe passive hyperemia. Capillaries in both glomeruli and interstitium of cortex and medulla showed congestion to a great extent accompanied by hemorrhages. Congestion of capillaries in medulla were observed even in cases with slight congestion. Renal tubules of all cases showed necrobiosis to various extent. Interstitium was edematous and often showed cell accumulation and infiltration. A part of the

interstitium in some cases had become fibrous, but very slightly. Some cases contained hyalinous substance in Bowman's capsules and contained multiple fibrin thrombi in the blood vessels (Nos. 1, 2 & 4).

Heart: Passive hyperemia, endocardial and epicardial hemorrhages and hemorrhages of intermuscular tissues and interstitial edema were observed. Some cases often showed conspicuous fibrinoid swelling of the walls of the arterioles (Nos. 9, 11 & 13). These changes were observed to become greater on the walls of small and middle sized arteries. One case (No. 9) showed hyalinous fibrosis on slightly thickened walls of the arteries.

Lungs: Generally congestive edema was conspicuous. The capillaries of the alveolar wall were severely dilated and showed a congestion taking zigzag formation. Interlobular connective tissue increased its thickness and become intensively edematous; lymph vessels were severely dilated containing serous contents. Some cases were accompanied by marked hemorrhages (Nos. 12, 13 & 16). Fibrin thrombi were often observed in the vessels (Nos. 1, 2, 3 & 10). At the same time, some cases showed slight acute catarrhal bronchitis and bronchiolitis (Nos. 9, 12, 14 & 16), broncho-pneumonia in an initial stage (No. 16) and subacute catarrhal bronchitis (No. 7). In one case (No. 4), proliferation of histiocytic cells was observed on the alveolar wall. One other case (No. 12) showed fibrinoid swelling on the walls of the blood vessels.

Lymph nodes: Showed blood resorption accompanied, in some case, by hemorrhages in the follicles. Lymph follicles were poor in cells and pale, and showed loosening. In some cases, reticulum cells in medulla were proliferated showing changes of catarrhal lymphadenitis (Nos. 7, 8, 9, 12, 13 & 15). Sometimes cell proliferation of medullary cord was well defined specially by occurrence of lymphoid cell proliferation (Nos. 14 & 15). Some cases contained fibrin thrombi in the blood vessels (Nos. 4 & 14) and showed fibrinoid swelling of the walls of the capillaries (No. 16).

Adrenal glands: These glands generally exhibited hyperemia which was outstanding in *Zona glomerulosa*, *Zona fasciculata*, and at the boundary portion of cortex and medulla. Some cases showed focal hemorrhages (Nos. 8, 9 & 12). In case No. 12, necrobiotic foci were formed in *Zona glomerulosa* and *Zona fasciculata* of cortex and accumulation was seen of neutrophil and eosinophil leucocytes at the same region. In case No. 14, fibrinoid swelling was observed on the walls of the capsule blood vessels.

Pancreas: Was congested and some showed interlobular edema.

Thymus: Severe hyperemia accompanied by focal hemorrhages. Interlobular connective tissue became edematous severely, increased its thickness, and showed hemorrhages. Activity of reticulo-endothelial cells and fibrin thrombi in the blood vessels were noted in case No. 14.

Tonsils: Hyperemia. Follicles were poor in cells and pale. Lymphoid tissues except follicles were rich in cells with partial cell proliferation.

Mucosa of nasal cavity: Marked hyperemia; lacunal dilatation containing a good many of fibrin thrombi. Infiltration of lymphocytes was found in the submucosa.

Larynx: Edematous and hyperemic submucosa.

Oesophagus: Marked hyperemia. Some showed relatively well defined submucosal and subserous edema, and some of the blood vessels contained fibrin thrombi.

Forestomach: Hyperemia and edematous submucosa.

Stomach: Well developed edema in the submucosa and subserosa. Congested *Tunica propria*. Cell accumulated foci in *Tunica propria* in case No. 9 and *Coccidium* in No. 8.

Small intestine: Edematous submucosa and subserosa. Hyperemia and cell infiltration in the *Tunica propria*. Hyperplasia of lymph follicles (No. 13), abscess formation in the *Tunica muscularis* (No. 5), fibrinoid swelling of the walls of the arteries of submucosa (No. 5), abscess formation in the submucosa accompanied by severe hyperemia (No. 9) and Coccidiosis (No. 16).

Large intestine: Edematous submucosa and subserosa. Hyperemia and *Coccidium* in *Tunica propria* (No. 5), fibrin thrombi in the submucosal blood vessels (No. 12), hyalinous thickening of the walls of the arteries in the *Tunica muscularis* and cell proliferation of adventitia (No. 9).

Urinary bladder: Edema was observed in *Tunica propria*, intermuscular tissues and subserosa. Edematous *Tunica propria* became congested. Subepithelial hemorrhages, which partly wedge into intermuscular tissues (Nos. 5 & 16). Case No. 5 showed multiple fibrinoid swelling on the walls of the blood vessels.

Skeletal muscles: Passive hyperemia. Partly exhibited myodegenerated foci. Muscle fibers changed its formation to masses of fragmentation and large histiocytic cells were accumulated (No. 7). In case No. 5, following changes were noted: hyalinization, vacuole formation, and fragmentation of muscle fibers without cell reaction; severe hemorrhages in the intermuscular tissues; well defined fibrin deposition accompanied by neutrophil leucocytic infiltration; fibrinoid swelling on the wall of the blood vessel (Fig. 7).

Testis: Interstitial hemorrhages in one case (No. 16).

Bone marrow: No outstanding changes other than occurrence of hyperemia.

Thyroid glands: Six cases were investigated all of which showed marked hyperemia, glandular epithelia increased their height taking cylindrical shape; colloid in the space of the follicles was either decreased, lost or changed into liquid. Glandular epithelia were desquamated in the space of the follicles and were packed with enlarged rounded epithelia. Some, however, showed papillomatous proliferation and in several layers.

Parathyroid glands: Only one case was examined. Hyperemia and interstitial edema were observed.

Hypophysis: Marked hyperemia, and subcapsular hemorrhages in some cases (Nos. 13 & 14).

Central nervous system: Degeneration and loss of granule cells ("Lichtung") was observed diffusely in the granular layer in the cerebellar cortex in all cases excepting No. 9. No conspicuous changes were observed in other brain area except in the perivascular cell infiltration was noticed in a part of meninges and encephalo-substance of the prosencephalon in case No. 13. Cells were composed mainly of lymphoid round cells and sometimes contained neutrophil and eosinophil leucocytes. Similar findings were

recognized in encephalo-substance of the prosencephalon and cerebellar meninges in case No. 16, but not so distinctly as in case No. 13. Eosinophilic granule substances were observed in the cytoplasm of medium sized nerve cells sited in the *Area vestibularis* of "Bodengrau" of the *Medulla oblongata* (Nos. 7, 13 & 14). Cerebrum showed slight hyperemia in some cases, but anemic and small hemorrhagic foci were observed in half of the cases. Small blood vessels rarely contained hyalinous thrombi.

Inasmuch as the cerebellar lesions were extremely characteristic, both decrease and disappearance of staining property of the granular layer could easily be identified macroscopically in the section preparations of the cerebellum except in case No. 9; the severity of lesions was most distinctive in the palaeocerebellum. Even under microscopy, as well as in macroscopical observation, it was confirmable that very severe desolation of the granular layer had taken place generally in the palaeocerebellum. On the contrary, the lesions were weakened to a certain extent in the dorso-lateral portion of the cerebellar hemisphere. Granule cells, starting with pycnosis, will finally become destructive followed by loss of cells taking the courses of hyperchromatosis, deformation of nuclei, irregularly stained nuclear substance, decrease in general staining property, ghost appearance, the formation of vacuoles and reticular structure in nuclei. From such changes "Lichtung" to various extents become distinctive. Silver impregnated preparations in no cases showed outstanding changes. The desolation of the granular layer was nearly limited to granule cells, whilst Golgi's cells and others were not damaged at all, but were relatively well maintained. Purkinje's cells also seemed to be in normal condition. The basket cells and small cortical cells in the molecular layer also did not show any change as was also the case in the perpendicular and transverse nerve fibers in the medulla. These conditions were also found in myelin sheath stained preparations. Even Sudan III stained preparations did not present the appearance of positive fat substance in any area. In addition to the above, the authors were unable to find any reactive changes resultant from such lesions in any of the cases.

DISCUSSION

What is the so-called "Kiryoi disease"? The occurrence of this disease is limited geographically to the mountainous regions in the Chugoku-Sanin area of Japan; it breaks out early in the pasturing season in May or June being contracted mainly by young cattle (2 years of age). As this disease outbreaks occur in remote pastures in mountainous areas, it is impossible to conduct detailed observation for the course of the disease and the majority of the animals are found as carcasses or in a moribund condition by owners. According to the reports made on this disease in the past^{7,9,10,17,24}, major symptoms to be cited are acute heart weakness, fall of the body temperature, staggers, syncope, paralysis or disappearance of skin sensibility, disappearance of reflex-function, and asthenia. Besides, nervous symptoms such as ataxia, somnolence, rotation of the ocular bulbus and clonic spasm are known to be serious symptoms.

It also seems that importance has also been placed on the role played by

external conditions such as geographical conditions, and sudden changes of season and weather (particularly the sudden exposure to cold weather^{7,9)}).

Up to date, intoxication²⁴⁾ (Nejiki poisoning), infection theory^{8,17)} and others have been discussed as causal factors, but such theories have recently been disproven. KAMOCHI, according to the reports prepared by an investigation team of the Ministry of Agriculture respectively in 1952 and 1953, interpreted "Kiryoi disease" of cattle as a collapse symptom of nutritional disturbances resulted from sudden changes of climatic conditions in mountainous and cold weather regions. UESAKA and his coworkers* tried to define the disease from the nutritional point of view but they could not reach a conclusion. ITAGAKI et al.⁷⁾ held that the disease was hypoglycemia which broke out during an infection of *Piroplasma* throughout their clinical investigations. However, inasmuch as such investigations were not based on synthetic pathological studies, the exact character of the disease is still obscure.

In this report is presented a description of pathological investigations conducted by the authors on the materials collected from 16 cases which were regarded as "Kiryoi disease". The central nervous systems were studied in 12 out of those 16 cases. Pathologico-anatomically, the following circulatory disturbances were conspicuous: congestive edema of the lungs, acute passive hyperemia of the spleen, passive hyperemia of the kidneys, dilatation of the right heart ventricle or ventricles of both sides, endo- and epicardial hemorrhages of the heart, passive hyperemia of the liver, interlobular edema in the thymus, congestive edema in the laryngeal portion, general anemia, and sometimes hydrothorax and ascites. In addition to the above, acute catarrhal broncho-pneumonia and bronchitis, enlargement of the lymph nodes, necrotic foci in the liver, and catarrhal gastro-enteritis were also observed often. The central nervous systems of the examined cases did not show any outstanding macroscopical change.

Throughout histopathological investigations, very characteristic changes were recognized in the central nervous system; that is, cortical cerebellar atrophy of granular type (degeneration) was noticed in 11 out of 12 cases investigated. Such changes were observed diffusely, but especially marked in the palaeocerebellum. Even though Purkinje's cells and Golgi's cells were relatively well maintained, the degeneration and the loss of granule cells were well defined and "Lichtung" was marked. Nerve fibers, however, were intact and did not manifest reactive changes. On the other hand, the authors found that circulatory disturbances which resulted from dysfunction of the heart and anemia had played an important role in the visceral changes. In short, there were noted: congestive edema of the lungs, acute passive hyperemia of the spleen, active and passive hyperemia

* Meeting of Jap. Zootechnical Sci. on April 7, 1952.

or hemorrhages of the liver, the kidneys, the heart and the adrenal glands, interlobular edema and hyperemia or hemorrhages of the thymus, blood resorption of the lymph nodes, and subserous and submucosal edema of the alimentary canal. The formation of fibrin thrombi was found in various parts; there were observed fibrinoid swellings on the walls of small and medium sized blood vessels of the heart, the liver, the spleen, the lungs, the lymph nodes, the adrenal glands, the alimentary canal, the urinary bladder, and the skeletal muscles. At the same time, the following changes which were regarded as associated ones were also observed: acute catarrhal bronchitis or broncho-pneumonia in an initial stage; catarrhal lymphadenitis; formation of focal necrosis and fine, or larger, cellular foci of the liver; slight activation of reticulo-endothelial cells; abscess formation in the alimentary canal; focal myodegeneration in the skeletal muscles; necrobiotic foci and cell infiltration of cortex of the adrenal glands and hyperplasia of follicles in the alimentary canal. In addition, in the thyroid glands of all the cases investigated, *struma parenchymatosa diffusa* was observed.

It can be said that what attracted the attention of the authors throughout the present investigation, of course, were the outstanding degenerative necrotic changes localized in the granular layer of the cerebellar cortex. In regard to the conception of the disease, as previously reported in detail by YAMAGIWA et al., it is apparent from the histological point of view that it should belong to the primary cortical cerebellar atrophy (degeneration) of granular type. Pertaining to such a disease of domestic animals which takes place in the cerebellum, there are a few reports which have been made^{3,4,5,6,16,19,22}, but they seem to be somewhat different from the authors'.

In the recapitulated report made by ULE²¹) concerning such a disease may a causal factor is presented. The authors find it difficult to conclude, as advocated by YAMAGIWA et al., whether or not such a type of disease originates from hereditary or familial, congenital and internal or external toxic factors. ULE²⁰) interpreted the cortical cerebellar atrophy of granular type as a manifestation of only one stage of a constant reactive form in the cerebellum caused by various factors, and etiologically not a nosological entity. As pointed out by YAMAGIWA et al., what attracts the attention of the authors is the cerebellar lesions which appeared in reported cases of LEIGH and MEYER and in one case of hypoglycemic coma which was cited in the report of ULE²⁰). Extremely fresh necrobiotic or necrotic changes of the granular layer of the cerebellum are somewhat similar to what was found in the cases subjected to authors' present investigation. In any way authors' cases can be considered morpho-genetically as extremely acute ones, because of no accompanying reactive changes, and because of lacking degeneration and break of nerve fibers.

The authors now would like to discuss the relation between the above described cerebellar changes and so-called "Kiryoi disease", but it is surprising that no definite explanation has so far been given of such nervous symptoms as ataxia, somnolence, rotation of the ocular bulbus, and atonic spasm, etc., even though the existence of such symptoms has been previously detected in serious cases of the disease. As the present cases did not provide clinical data in any case, it makes impossible a comparison directly with clinical findings. In consequence, the possible appearance of some sort of symptoms subsequent to the formation of outstanding lesions of the cerebellar cortex can only be imagined. The authors would like to forebear from going into any full discussion on connections which may exist between the cerebellar lesions and functional localization.

On the contrary, the authors would like to discuss the significance of the non-appearance of cerebellar lesions in one (Case No. 9) out of 12 cases. From the facts presented above, it is learned careful consideration must be given when discussing whether or not so-called "Kiryoi disease" always has to be accompanied by cerebellar lesions or when deciding whether or not those lesions could be different from each other. In this regard, the authors would like to call attention to the fact that the disease has rarely been found in adult cattle, even in stable animals and in seasons other than spring, and that the majority of animals infected with the disease can be restored to health by means of symptomatic treatment.

The authors here-below would like to discuss the significance of the visceral changes, considering the role played by the changes in the central nervous system. Each of the cases seems to have manifested an acute deficiency of oxygen based on circulatory disturbances which originated from dysfunction of the heart and anemia, according to what information the visceral changes indicated. In other words, the following circulatory disturbances seem to play a main role: congestive edema of the lungs; marked passive hyperemia of the liver; dilatation and edema of Disse's spaces of the liver; vacuolar degeneration of hepatic cells; subserous and submucosal edema of the alimentary canal; interlobular edema of the thymus; and formation of multiple fibrin thrombi and other disturbances. The authors, therefore, consider that the sickness develops into hypoxemia caused by circulatory disturbances, and finally causes collapse subsequent to the reduction of basic metabolism. As evidence of hypoxemic collapse pointed out by BÜCHNER, dilatation of Disse's spaces can be detected under microscopy as an increased permeability of the capillary walls. The fact that fibrinoid swelling of the walls of the blood vessels was so often observed throughout the cases studied in the present investigation should be interpreted as a noteworthy change. The authors are not able to conclude which one whether infectious, toxic, allergic, or edematous changes or the metabolic disturbances should be the principal factor. Emphasis

should, however, be laid on the role played by edematous changes, on the basis of changes manifested in the present cases. At any rate, it is obvious that such changes impede the activity of the cardiovascular system both functionally and morphologically. Such hypoxemic changes accompanied by heart weakness can be considered as one of the factors causing death, because of the fact that acute heart weakness has often been found clinically to play an important role in this disease.

In addition to the above mentioned changes, such associated infectious changes as acute catarrhal bronchitis, necrotic foci and cellular foci of the liver, catarrhal lymphadenitis of the lymph nodes, and activity of reticulo-endothelial system are observable in present cases. (The authors might note that the conception of the existence of some primary infection which had been thought as the cause of the disease is no longer acceptable.) The authors would like to interpret such changes just as in the case of the way by an individuals may be affected secondary infection when their power to resist the infection becomes weak on account of being in collapse state and being exposed to cold weather. Therefore, there is a possibility that such changes may join the changes previously described to create a death factor. The infectious changes shown in the present cases are relatively slight ones and could not be considered as primary changes judging from an over-all view of all of the cases.

The finding that *struma parenchymatosa diffusa* was recognized in all of the cases investigated would be of much interest when the geographical environment of areas where so-called "Kiryoi disease" breaks out is taken into consideration. It is a well known fact that the thyroid glands play a decisive role in the maintenance of the body temperature. According to recent studies^{13,14,15)}, it is revealed that a histologically constant change takes place in the thyroid glands as a result of the basic metabolism in the body and requires more consumption of heat-producing substances such as carbohydrates. Such a phenomenon invites the exhaustion of glycogen of the liver, the skeletal muscles, the heart muscles and other parts at the same time as the declination of the body temperature, which leads finally to exhaustion of glycogen stored in the body and then causes hypoglycemia¹⁾. It is understood in such a case that, in order to maintain the body temperature, the disappearance of colloid in the thyroid glands, hyperfunction, deformation of follicles, hyperemia and epithelial proliferation take place inasmuch as a large quantity of thyroxin from the thyroid glands is required to be supplied; these events morphologically lead to manifestation of *struma parenchymatosa* lacking in colloid after all as a hyperthyroidism.^{13,14,15)}

As for "Kiryoi disease", sudden changes of weather, (about 20°C difference between day and night: maximum in day time, 25°C, and minimum at night,

around 0°C an average) particularly exposing animals to cold weather, have been considered important as a causal factor of this disease. The facts that hypoglycemia is clinically observed and cerebellar changes resemble ones in case of hypoglycemic coma, however, attract one's attention though it might not be safe to discuss causes on the basis of that similarity.

According to TAKAMORI, goiter has been found endemically in the Nagano Prefecture area of Japan with *struma parenchymatosa diffusa* being found the most. The authors, therefore, suspect that goiter in cattle may also have been occurring very often in the area, epidemic in "Kiryoi disease", and at the same time the authors should not fail to consider that the cattle suffering from "Kiryoi disease" become hypoglycemic state. The cases taken up in the present investigation are respectively 2 years old animals and it seems that this goiter is not new-born-animal-goiter but belongs to the goiter type in growing or adult animals. According to TAKAMORI, workers should be well aware of the fact that thyroid enlargement and histological findings do not always agree with each other.

Every one of the materials examined by the present authors, as described in this report, were obtained from the cases regarded by the owners, in the sites, as so-called "Kiryoi disease". Clinical data was not available. Thus, before reaching any conclusion as to whether or not the disease so far called "Kiryoi disease" is nosologically properly classified as the same as the authors' here described sickness and is really independent disease entity, much careful discussion will have to be conducted.

In any case, the authors will be encouraged if the present studies provide any fundamental suggestions for study on "Kiryoi disease" in the future.

CONCLUSION

Conducting pathological investigations on cases regarded as so-called "Kiryoi disease", the authors detected in most cases (excepting one case) primary cortical cerebellar atrophy (degeneration) of granular type in the central nervous system. The study also seemed to have revealed that circulatory disturbances centering around the dysfunction of the heart and anemia had played a main role in causing visceral abnormalities. As associated changes, infectious changes were often observed. In addition to the above, *struma parenchymatosa diffusa* was observed in all the cases investigated. The discussion contained in this report pertains to the relation between such changes and so-called "Kiryoi disease".

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EXPLANATION OF PLATES

PLATE I

- Fig. 1. Case No. 8. (Pr. 483): Congestive edema and interlobular edema of the lung. Hematoxylin-eosin stain (H.-E.), $\times 65$.
- Fig. 2. Case No. 10. (Pr. 571): Acute passive hyperemia of the spleen. H.-E., $\times 65$.
- Fig. 3. Case No. 11. (Pr. 573): Interlobular edema of the thymus. H.-E., $\times 65$.
- Fig. 4. Case No. 2. (Pr. 177): Fibrin thrombus in the kidney. H.-E., $\times 140$.

PLATE II

- Fig. 5. Case No. 11. (Pr. 573): Fibrinoid swelling of the wall of the artery in the heart. H.-E., $\times 280$.
- Fig. 6. Case No. 13. (Pr. 643): Fibrinoid swelling of the wall of the artery in the heart. H.-E., $\times 280$.
- Fig. 7. Case No. 5. (Pr. 353): Fibrinoid swelling of the wall of the artery in the skeletal muscles. H.-E., $\times 280$.
- Fig. 8. Case No. 5. (Pr. 353): Fibrinoid swelling of the wall of the arteriole in the liver. H.-E., $\times 280$.
- Fig. 9. Case No. 13. (Pr. 643): Blood resorption in the *Ln. bronchialis*. H.-E., $\times 65$.
- Fig. 10. Case No. 13. (Pr. 643): Slight activity of reticulo-endothelial cells in the *Ln. mesentericus*. H.-E., $\times 280$.

PLATE III

- Fig. 11. Case No. 9. (Pr. 488): Focal necrosis in the liver. H.-E., $\times 140$.
- Fig. 12. Case No. 16. (Pr. 651): Cellular focus in the liver. H.-E., $\times 140$.
- Fig. 13. Case No. 16. (Pr. 651): Bronchitis catarrhalis acuta. H.-E., $\times 65$.
- Fig. 14. Case No. 13. (Pr. 643): Struma parenchymatosa diffusa. H.-E., $\times 130$.

PLATE IV

- Fig. 15. Case No. 14. (Pr. 649): Decrease and disappearance of staining property of granular layer can easily be identified macroscopically with the section preparation of the cerebellum. H.-E., $\times 2.8$.
- Fig. 16. Case No. 15. (Pr. 650): Slight degeneration and loss of granule cells in the cerebellar cortex. H.-E., $\times 260$.
- Fig. 17. Case No. 4. (Pr. 289): Degeneration and loss of granule cells ("Lichtung") in the cerebellar cortex. H.-E., $\times 260$.
- Fig. 18. Case No. 12. (Pr. 582): Marked degeneration and loss of granule cells ("Lichtung") in the cerebellar cortex. H.-E., $\times 260$.







