A NEURO-HISTOLOGICAL AND NEURO-PATHOLOGICAL STUDY OF THE PANCREAS

by

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(Received for publication Aug. 10, 1959.)

Content

1. INTRODUCTION

BOEKE, STOEHR, SUNDER-PLASSMANN, JABONERO and others reported the terminal structure of the vegetative nervous system. According to their opinions, the terminal structure of the vegetative nerves usually form a terminal nervous network with SCHWANN's Syncytium like the vascular capillary nets without terminating freely at least in the analysis with light microscopy.

On the other hand, SETO, H. discovered free ending thick nerves in viscera, which were defined as visceral sensory nerves by SETO.

These SETO's visceral sensory nerves were found by many investigators of our clinic in all other portions of the alimentary canal. They proved their sensory nature by degeneration experiments with the resection of the roots of spinal cord and vagotomy.

The author can find few reports on neuropathological change in the tumor of the alimentary canal except YAMADA (1957), SEKIYA (1958) and HAKODA (1959) who found clear degeneration picture, in cancer of stomach, in cancer of the tongue and the rectum, and in viscera infiltrated by YOSHIDA tumor cells, respectively.

SETO, H. and HAGEN, E. and others reported on the nervous innervation of the pancreas from neuro-histological standpoint. However the author can not find on the neuro-pathological study of cancer of the pancreas which causes sometimes severe abdominal pain. The author studied neuro-histologically and neuro-pathologically on the sensory and vegetative nerve endings in the normal and carcinomatous pancreas and tried to clarify the clinical symptoms in the patients with cancer infiltration of the pancreas.

2. MATERIALS AND METHODS

The materials used in the present study were the pancreas of human beings and dogs. The author used only fresh specimens taken from the pancreas which were resected operatively. After fixation for 3–4 weeks in 10 % neutral formol solution, the specimens were frozen, sliced thickness of 30–35, fixed again in 10 % neutral formol solution for more than 4–5 months, and then were stained. The axiscylinder was stained with SETO's modification of Bielschowsky's silver impregnating method.

SETO's method

The specimens, which have been sliced with the freezing method and kept in 10 % neutral formol solution, are

1) washed with distilled water for a few minutes.
2) put into 20 % silver neutral solution, being protected from light, for 24–48 hours,
3) washed in distilled water for 20–30 seconds.
4) put into 20 % neutral formol solution.
   This solution should be made by diluting the mother neutral formol only with running water, and placed in 4 plates. And then the specimens are transferred one by one until the white precipitation disappears.
5) washed with running water for 30–50 seconds,
6) placed on filter paper to blot up the water,
7) immersed in warm ammoniacal silver solution for about 10 minutes.
8) washed with distilled water twice,
9) placed in 0.05–0.1 % gold chloride solution for 3–4 hours,
10) washed in distilled water for a few minutes,
11) placed in 20 % sodium thiosulfate solution until the specimens are colored reddish brown,
12) washed in distilled water,
13) dehydrated and mounted.

3. MICROSCOPICAL OBSERVATIONS ON THE NERVES OF THE NORMAL PANCREAS

The neuro-histological study was done on the normal pancreas of the adult dogs. The nerve bundles and isolated fibers enter into the exocrine portions and the narrow interlobular connective tissue (Figs. 1, 2 and 3). Figs. 4, 5, 6 and 7 show the fine nervefibils with Schwann's nuclei along the vessels in the exocrine portion. Throughout the specimens, they do not terminate in free ending, but their neurofibrils form a fine network in runing around exocrine gland cells.

But the author could not observe the delicate fine network as E. HAGEN described.

Figs. 8, 9, 10 and 11 show the thick nerve fibers in the exocrine portion. These thick nerve fibers showed a characteristic thickness with windings and varicosities

on the courses (Fig. 12).

They were easily distinguished from the fine network of the autonomic nerve fibers. They had a form of ending identical with the sensory nerve fibers described by H. SETO.

These thick nerve fibers terminate freely in the wall of the interlobular blood vessels and the exocrine gland cells.

These thick nerves gradually decrease their thickness afid terminate as a tapering endings (Figs. 13, 14 and 15). Occasionally, some showed arborization, circular terminal course (Fig. 16) or a loop near the termination. (Fig. 17.)

Honever, the author could not find a specific nervous end apparati in the pancress.

In all portions there were the ganglion cells scattered in small groups, most of them are found in the interlobular connective tissue on the head of the pancreas (Figs. 18 and 19). A small ganglion with a few nerve cells (Fig. 20) are found beside interlobular blood vessels, but they are not observed near or within the island of Langerhans as described by E. HAGEN. These nerve cells had bipolar and multipolar structures.

Figs. 21 and 22 show the nervefibrils with the plasma cord (Flasma strang by Stöhr) run into the island of Langerhans.

In each island of Langerhans, there were 10–20 of argyrophile cells. Most of them were in the island, but a few lay out-side of the island.

The fine nerve fibers with SCHWANN's nuclei came to the border of the island, reached the argyrophile cells, and other branches ran into the island. (Figs. 23, 24 and 25)

The author found some special affinity of the autonomic nerve fibers to the argyrophile cells in the nervous distribution of the island.

4. NEURO-PATHOLOGICAL OBSERVATIONS ON THE NERVES IN CANCER OF THE PANCREAS

Neuro-pathological changes were studied in a carcinoma simplex of pancreas, which obtained from an adult female patient in the late stadium of gastric cancer with carcinomatous infiltration of the pancreas.

As stated by YAMADA and SEKIYA of our clinic, two types of the nervous changes were observed in the surrounding and central area of cancers, respectively.

a) Change in the surrounding area of Cancer.

The neuro-histological change in the surrounding area is similar to that of chronic inflammation.

Fig. 26 shows two thick nerve fibers run across the field with nodular swellings and hyperchromasia. However, many nerve fibers (Figs. 27 and 28) and nervebundles (Figs. 29 and 30) were in almost normal in the marginal portion of cancer.

Fig. 31 shows a ganglion cell with a slight disharmonic change of nerve

process near the carcinomatous cells.

The vegetative fine nerve fibers forming a network were not observed in surrounding area of pancreatic cancer.

b) Change in the central area of cancer of the pancreas.

At the center of the cancer tissues, various, pathological changes were found. First of all, no nervous syncytium or terminal nerve network was found in the cancer tissues.

Figs. 32 and 33 show the nerve fibers having almost normal appearances. They ran through the cancer tissues without hyperchromasia or nodular swellings.

Figs. 34 and 35 show normal course of the nerve fibers running through the cancer cells along the blood vessels. Sometimes, the nerve fibers in a bundle came loose and detoured (Fig. 36).

Some small calibered fibers in a bundle were almost disappearing (Figs. 37, 38 and 39), while others had partial swellings in carcinomatous cell infiltration. The nerve fibers took a winding course around cancer cell groups, and some of them had, between cancer cells, nodular swellings, granules and vacuoles (Fig. 40).

As is shown in Figs. 41 and 42, at the center of the cancer tissues, the neurofibrils took irregular courses, showed detours, which had simetime an apparent severance on the section. The fine nerve fibers had a tendency to disappear earlier in the growth of the cancer tissues (Figs. 37, 38 and 39).

Figs. 43 and 44 show the nerve fibers running along the blood vessels at the center of carcinoma simplex. They became loose in a bundle and had a markedly winding courses. However, degenerative changes were not observed in the thick nerve fibers after disappearance of fine nerve fibers.

Fig. 45 shows ganglion cells at the center of the carcinomatous tissues. Some of them already disappeared and left only faint marks (1), and some others had dislocated (2) or shrinked unclei (3).

The author could not find the argyrophile cells in the island of Langeshans in the center of cancer.

5. DISCUSSION

In regard to the peripheral structure of autonomic nerves, BOEKE, STOEHR, SUNDER-PLASSMANN, JABONERO and others have described many morphological studies. Summarising their opinions, the autonomic nerve fibers usually form a fine network within the Schwann's syncytium in the periphery and they have not free terminations at least in a light microsocpical observation.

Recently, YAMAMOTO of our laboratory discovered free nerve endings in the smooth muscle of appendix in his electron microscope study and he concluded that these autonomic endings may not be possible to be found by a light microscope. According to YAMAMOTO, the SCHWANN's cells have cell borderings in the arrangement along the autonomic nerve fibers and never form a syncytium, but the present author describes them as a nervous syncytium (JABONERO) or Leit-

plasmodium (STÖHR), because he cannot discuss here beyond the light microscopy.

On the other hand, SETO, H. found free-ending thick nerves in the esophagus, stomach, duodenum and the anus in the light microscopical observation.

He maintains these nerves are the visceral sensory nerves with free endings, because their peripheral structures are morphologically similar to those of the somatic sensory nerves.

Histological studies of the sensory nerve in various viscera have beeen reported by many investigators of our clinic; i. e., TANAKA in the esophagus, OTSU in the stomach, INOUE in the biliary tract, MAKINO in the small intestine and in the cecum, Wang and Lee in the sigmoid and rectum, SATO in the ovary and OTSUJI in the testis.

In agreement with these opinions, the author sought for the sensory nerve in the pancreas.

The author's study in the pancreas came almost to the same results as them.

The author found thick nerve fibers with free nerve endings in all portions of the pancreas, except in the island of Langerhans. These thick nerves show simple shaped or arborized terminations as SETO described as a special character of the visceral sensory nerve.

In general, sensory nerve endings are considered to form a complicated structure or specific end-apparati, such as the VATER-PACINIAN, MEISSNER's or KRAUSE's corpuscle.

However, the author could not find such form of sensory endings in the pancreas.

Neuro-pathological changes in cancer have been reported by YAMADA in cancer of the stomach and by SEKIYA of the tongue and rectum. YAMADA reported that the changes of the nerve are divided into two kinds, i. e., the changes in the surrounding and the central area of cancers. According to him, change of the nerves in the surrounding area is similar to that of chronic inflammation and a characteristic change is found in the center of cancer.

The author observed the nerves in these two regions in cancer of the pancereas.

The author found only almost normal nerve fibers in the surrounding area of the pancreatic cancer, whereas he observed degenerated nerve cells and nerve fibers in the carcinomatous infiltration.

As YAMADA stated, some nerve fibers took irregular courses in the appearance of tumor cells.

The small calibered nerve fibers are less resistant in cancer. However, as SEKIYA reported, some nearly normal nerve fibers were found in the cancer tissues.

The author considers that the degenerated nerves or detoured courses of the nerve fibers are not caused by the only appearance of cencer cells, but they must be due to the special development and arrangment of the cancer cells.

None of the peripheral network of autonomic fibers with SCHWANN's plasmodium, which were called by STOEHR as the "PLASMASTRNG" and by JABONERO as the "nervous syncytium" were observed in the center of cancers.

The fine nerve fibers of the pancreas have a tendency to disappear earlier than thick ones in the growth of cancer tissues.

The early disappearance of the peripheral autonomic nerve fibers and the fine nerve fibers in the center of cancers may be due to the weaker resistance against cancer. The resistance seems to be parallel with the thickness of the nerve fibers.

The nerve cells are degenerated in cancer infiltration finally to destroyance of the cell body.

None of argyrophile cells in the island of LANGERHANS was observed in the center of cancer.

The disappearance of the argyrophile cells in the island of LANGERHANS in cancer can be attributed to the growth of the cancer tissues. The endocrine function in the pancreas must be distrubed in early stage of cancer infiltration by the lack of argyrophile cells.

6. SUMMARY AND CONCLUSIONS

Using BIELSCHOWSKY's methods modified by SETO, the author studied the nerves and their endings in the normal and pathologic pancreas of human beings and dogs. Summarizing the results following conclusions are obtained.

1) Sensory nerve endings are simple tapering or bifurcated free ending terminations in the pancreas.
2) No sensory nerve endings with a complicated structure or specific end apparati are observed in the pancreas.
3) The peripheral structure of the vegetative nervous system with SCHWANN's plasmodium are observed inthe pancreas of dogs.
4) The ganglion cells can be observed scattered in all portions of the pancreas of dogs, above all on the head of the pancreas.
5) The autonomic nerve fibers run near or into the argyrophile cells in the island of Langerhans.
6) The peripheral autonomic nervous structures and the fine nerve fibers disappear in the early stage of cancer.
7) The nerve fibers in cancer of the pancreas (carcinoma simplex) detour the cancer cells and choose their way along the stroma.
8) Sometimes, the nerve fibers run without showing any degenerative changes in the center of the cancer tissues.
9) The nerve cells in the cancer are degenerated and gradually destroyed.
10) The nerve fibers are resistant against the cancer infiltration paralleled with their thickness.
11) The thick sensory nerves in the pancreas can remain in cancer, which suggest the severe pain in the late stadium of the pancreatic cancer in-

filtration.

12) The argyrophile cells in the island of LANGERHANS disappear in the early stage of cancer.

I am much indebted to Assist. Prof. Dr. Ch. KIMURA for his kind guidance throughout this study.

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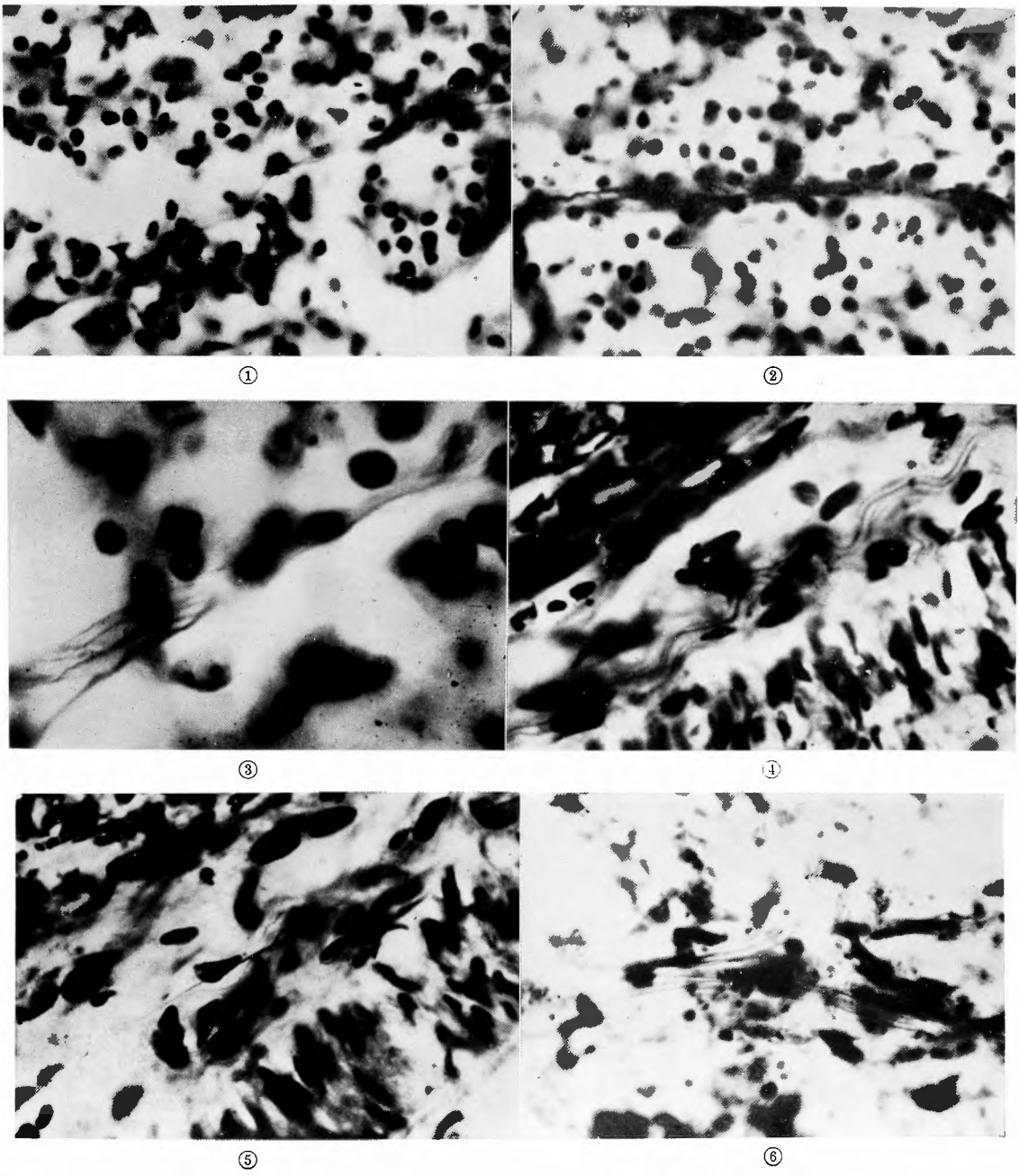


Figs. 1 and 2

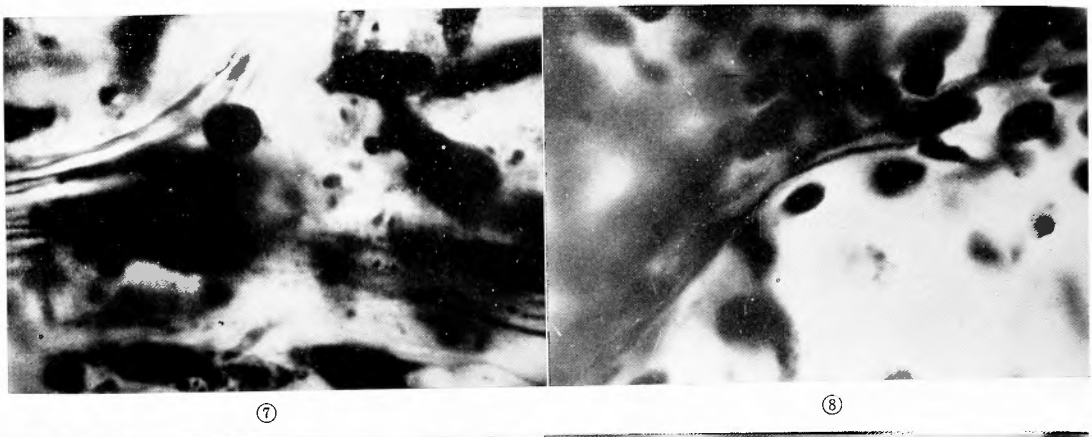
The nerve fibers running along the interlobular connective tissue (Dog) x 600 Bielshowsky's silver impregnation

Fig. 3

The same picture as Fig. 1. × 1,500

Fig. 4, 5 and 6

The nerve fibers running along the blood vessels. (D) x 600 B.



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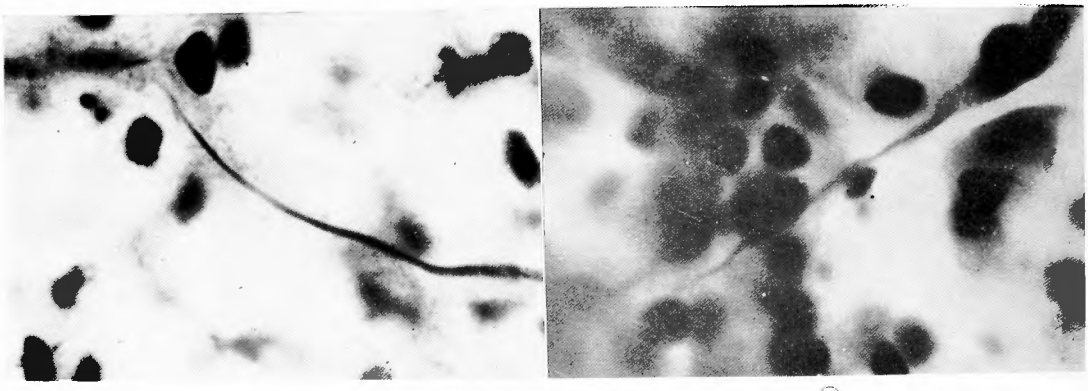

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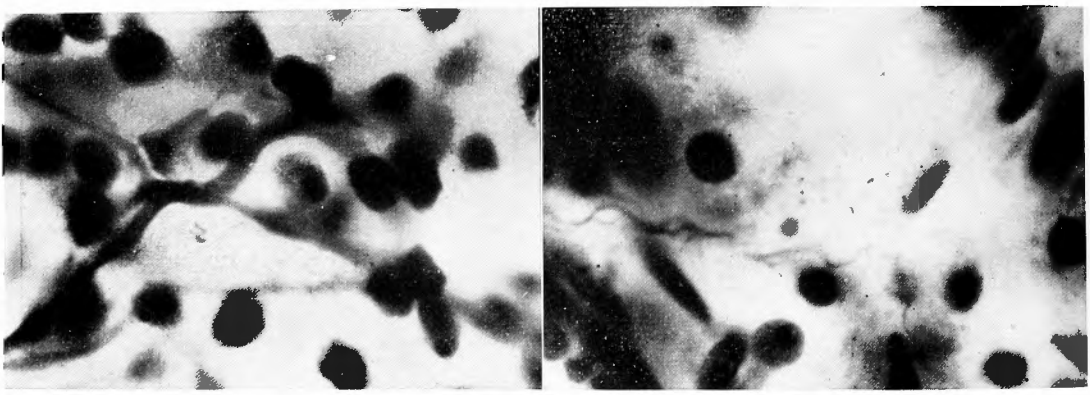

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Fig. 7

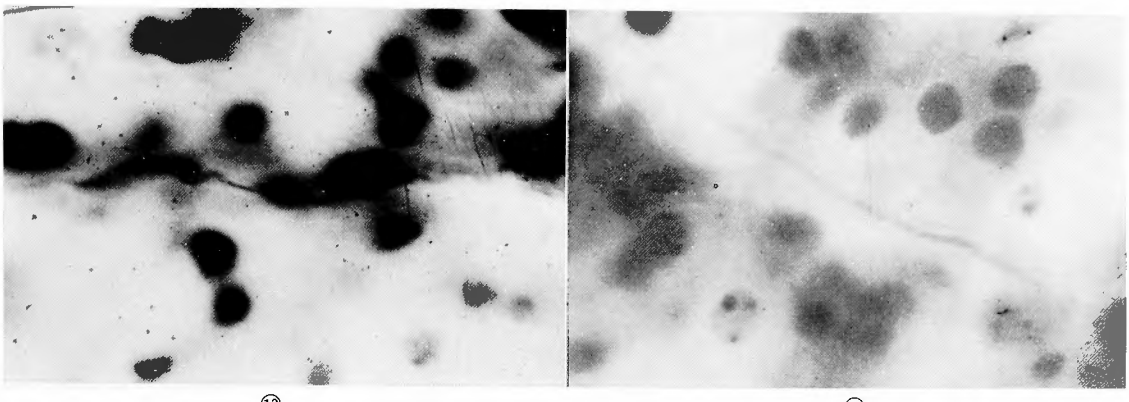
Enlarged picture of Fig. 6 x 1,500

Figs. 8, 9, 10 and 11.

A thick nerve fiber in the exokrine portion. (D) x 1,500 B.

Fig. 12

A nerve termination with the duplication and varicosites in the exocrine portion. (D) x 1,500 B.



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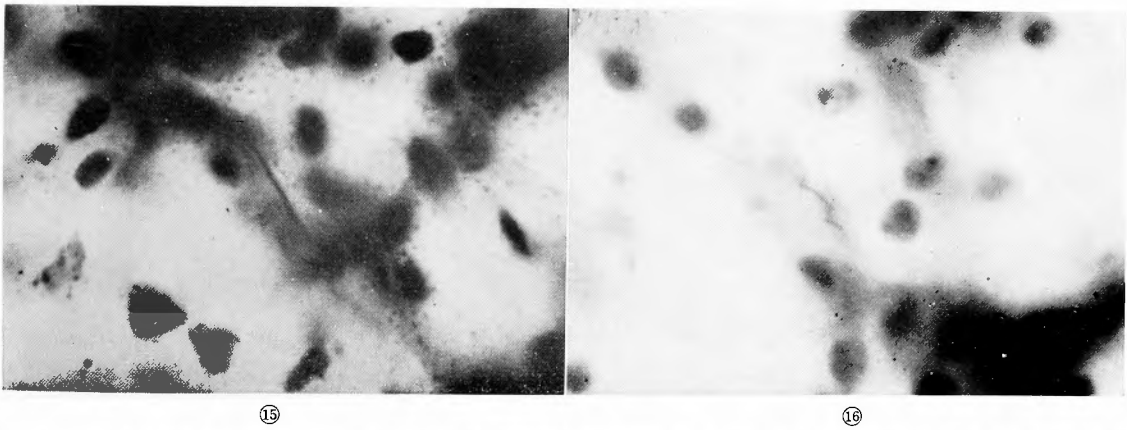

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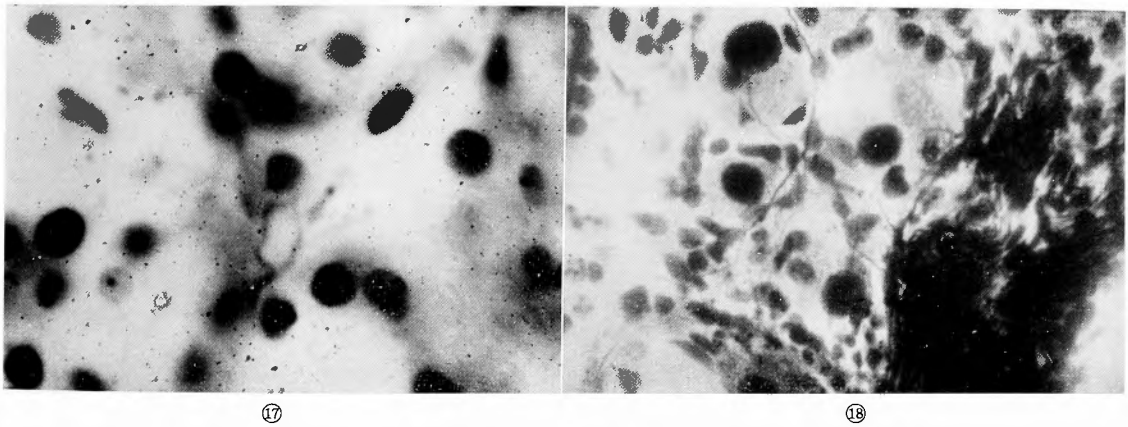

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Figs. 13, 14 and 15

Nerve terminations in tapering endings in the exocrine portions. (D) × 1,500 B.

Fig. 16

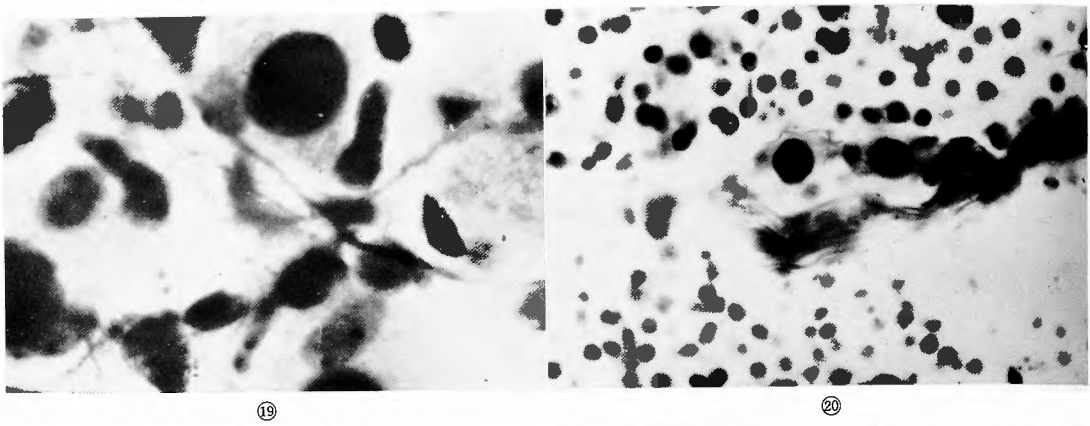
A nerve ending shows circular course in the exocrine portion. (D) × 1,500 B.

Fig. 17

A nerve with a loop-like ending in the exocrine portion. (D) × 1,500 B.

Fig. 18

The ganglion cells in the interlobular connective tissue in the head of the pancreas. (D) × 600 B.



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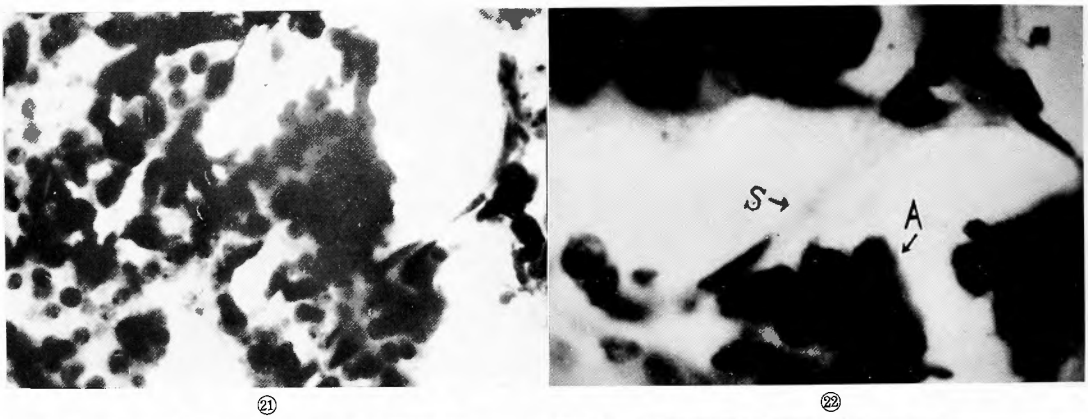

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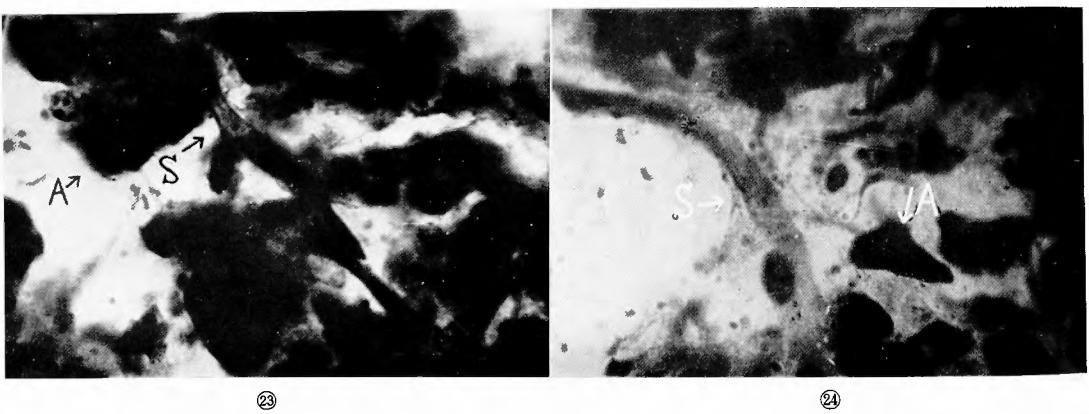

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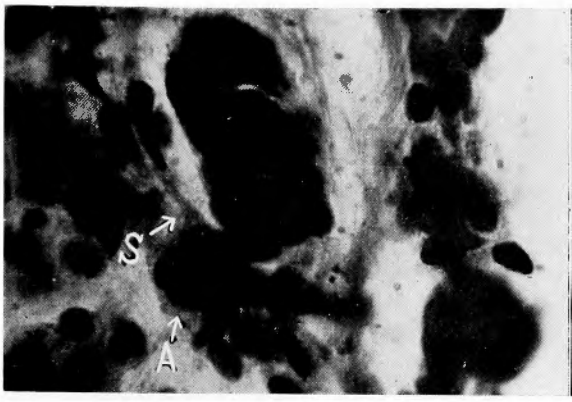
Fig. 19
Enlarged picture of Fig. 26 × 1,500

Fig. 20
The ganglion cells in the exocrine portion in the head of the pancreas. (D) x 600 B.

Fig. 21
Nervefibers in a nervous syncytium entering the island of Langerhans. (D) x 600 B.

Figs. 22, 23, 24 and 25
The nerve fibers with Schwann's nuclei came to the border of the island, reached the argyrophile cells (dark) and other branches ran into the island. (D) x 1,500 B.
(A : argyrophile cell of the Island of Langerhans, S↗ : a nervous syncytium.)



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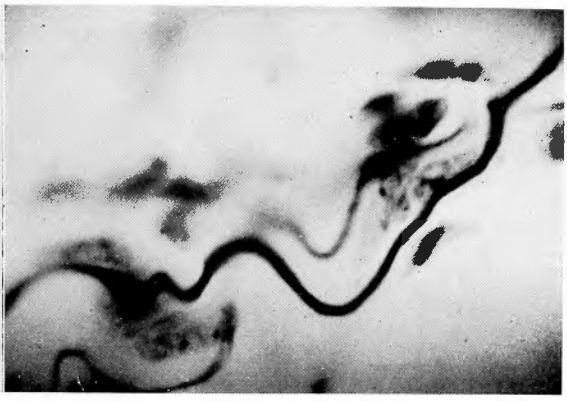

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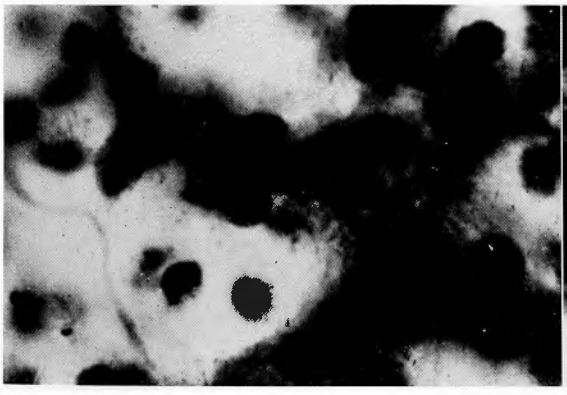

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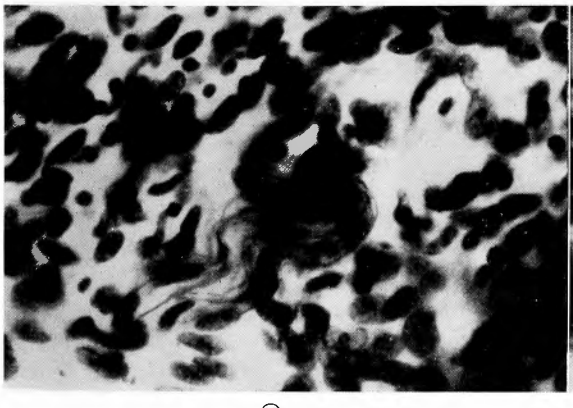

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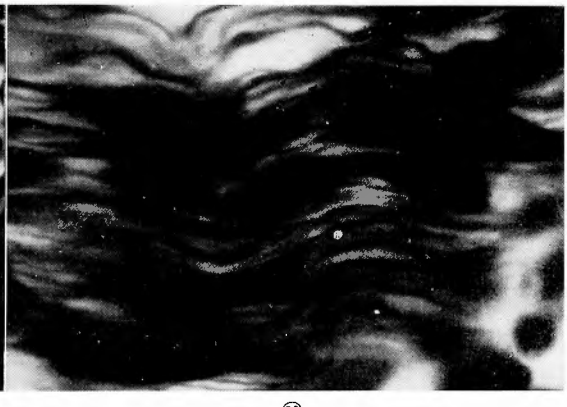

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Fig. 26

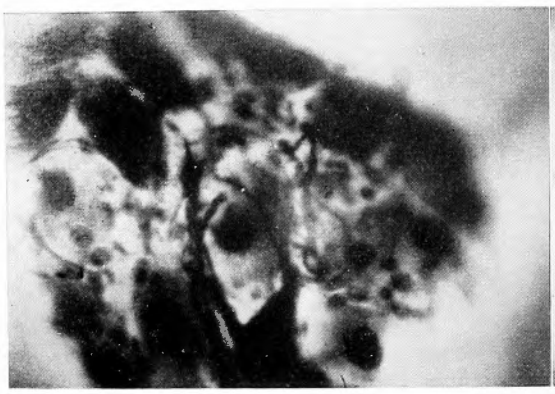
2 thick nerve fibers with nodular swellings and hyperchromasia in a surrounding area of cancer. (Human being) x 1,500 B

Figs. 27 and 28

The normal nerve fibers in the surrounding area of cancer. (H) x 1,500 B.

Figs. 29 and 30

The normal nerve bundles in the surrounding area of cancer. (H) x 1,500 B.



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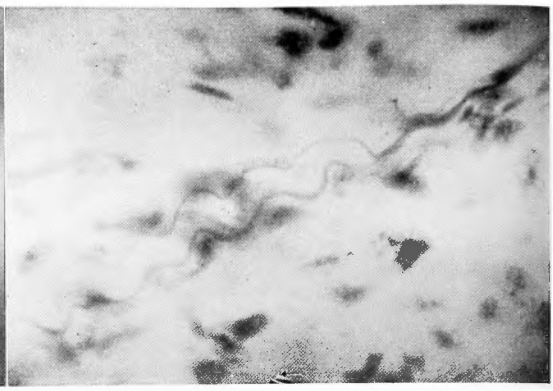

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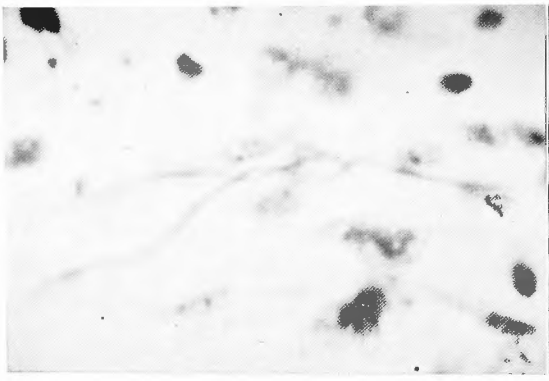

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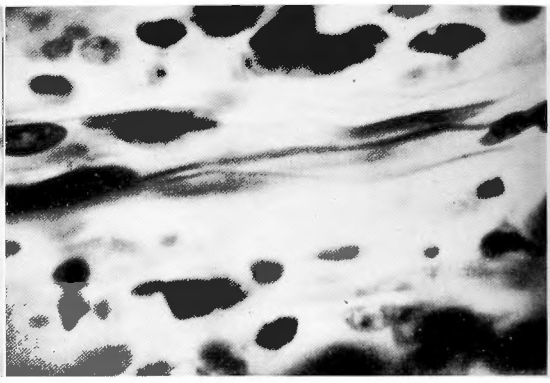

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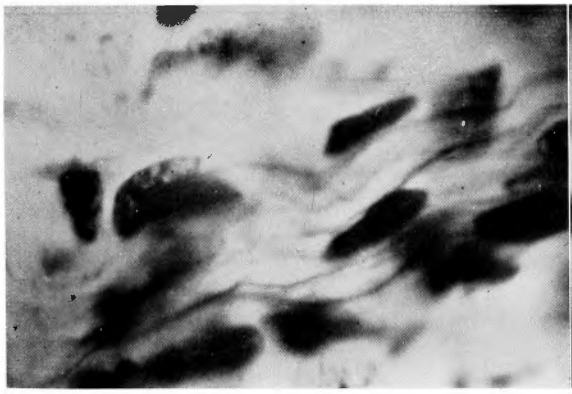
Fig. 31
Almost normal ganglion cells near the cancer tissue. (H) x 1,500 B.

Figs. 32 and 33
Almost normal nerve fibers running through the cancer tissue without any hyperchromasia and swelling. (H) x 1,500 B.

Figs. 34 and 35
Normal nerve fibers running through the cancer cells along the blood vessels. (H) x 1,500 B.

Fig. 36
The arrangement of the nerve fibers in a bundle becomes loose and undulated in a central area of cancer. (H) x 1,500 B.



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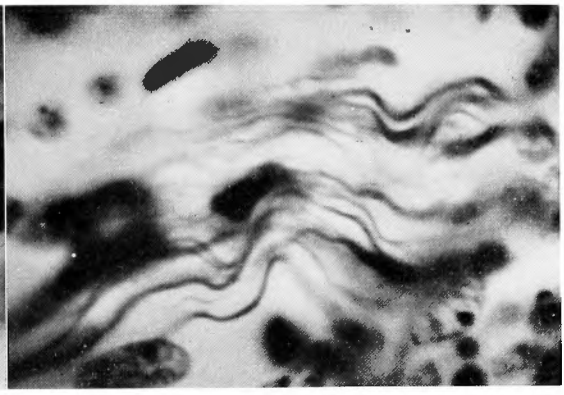

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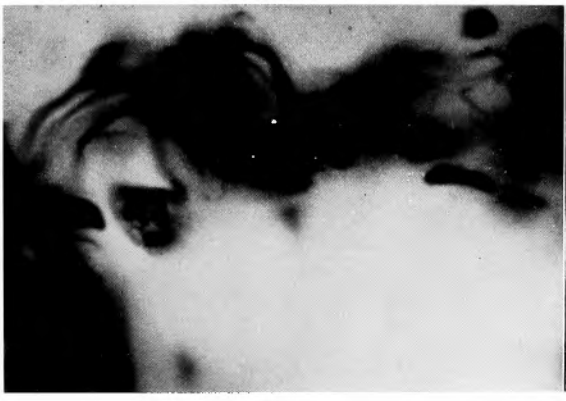

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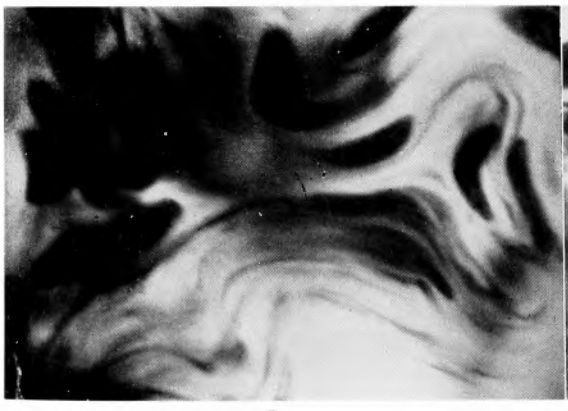

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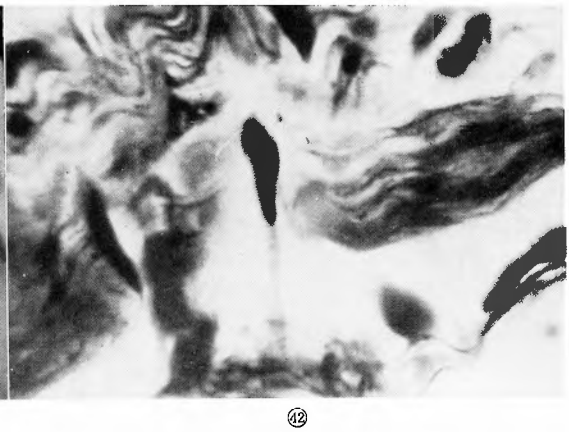

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Figs. 37, 38 and 39

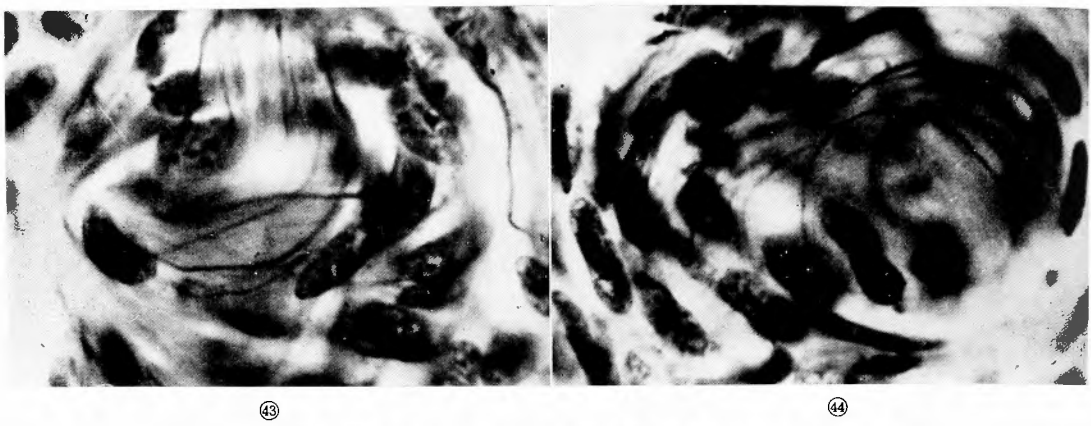
A central area of cancer. A nervebundle makes a detour by cancer cells. (H) x 1,500 B.

Fig. 40

A nerve fiber makes a detour by the growth of cancer cells and shows nodular swellings and vacuols and granules (H) x 1,500 B.

Figs. 41 and 42

The fine nerve fibers have a tendency to disappear and neuro-fibrils to take irregular courses in the center of cancer tissue. (H) x 1,500 B.



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Figs. 43 and 44

In the center of the cancer tissues, the nerve fibers become loose and shows marked winding courses. (H) 1,500 B.

Fig. 45

The nerve cells in the central area of the cancer tissue. Nerve fibers are arranged irregularly. (H) 1,500 B.

A nerve cell has already disappeared leaving a faint mark (1), some others show dislocated (2) or shrinked nuclei (3).

和文抄録

膵臓に於ける神経組織学的並に神経病理学的研究

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大 島 整

Bielshowsky 氏 神経鍍銀法の瀬戸氏変法を用いて犬の新鮮なる膵臓の標本及び成人の膵単純癌に於て神経の形態及びその分布更にその病的変化を追求し次の結論を得た．

1）犬の膵臓に於ける知覚神経終末は単純性又は分岐性游離終末を示し，外分泌部細胞間並に小葉間血管壁に認められたが，内分泌部には認められなかつた．

2）犬の膵臓に於て知覚神経の特殊終末形式は見出されなかつた．

3）犬の膵臓に於て外分泌部細胞間に神経シンチチウムを有する多数の自律神経終末構造を認めたが，一部は内分泌部即ち島内にも見出された．

4）犬の膵臓に於て神経細胞は内分泌部を除いたあらゆる部分に散在したが，その大部分は膵頭の小葉間結合組織内に見出された．

5）犬の膵臓に於て各ランゲルハンス氏島内に10～20個の嗜銀細胞を認めたが，小数のものは島外にも見出された．而して自律神経線維はランゲルハンス氏島の辺縁部を走り，一部は嗜銀細胞に達し，更に他の線維は島内に侵入しているのを見出した．即ちランゲルハンス氏島内に於ける神経分布に於て自律神経線維と嗜銀細胞は特殊な関係を有する如くである．

6）膵臓の単純癌に於て自律神経の終末構造並に細い神経線維は早期に消失する．

7）山田の言うように膵臓癌に於ける神経線維は癌細胞の周囲を迂回し軟かい基質を選んで走る様な形態を示すものもあるが，

8）膵臓の単純癌の中心部に於て時には何等の変性を示さない神経線維の存在を見出した．

9）膵臓の単純癌の中心部に於て神経細胞は核の転移並に収縮等の変性を呈し漸次に破壊されてゆく有様が見出された．

10）膵臓の単純癌に於ては，神経線維は癌細胞の浸潤に対して線維の太さに比例した抵抗を示した．

11）膵臓の単純癌に於て太い知覚神経線維が癌組織中に残存し得ることは膵臓癌の末期に於ける激しい疼痛を示唆するものであろう．

12）ランゲルハンス氏島内の嗜銀細胞は癌の早期に消失する．