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Experimental Studies on Nerves in Regenerated Liver

by

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CONTENTS

I. INTRODUCTION

Hepatic lobectomy is the only radical maneuver for such surgical lesions of the liver as malignant neoplasms or intrahepatic parasites. In recent years, as the experience of surgical treatment for hepatoma has been gradually accumulated, it has been eagerly desired to carry out reliable extensive hepatic lobectomy for improvement of surgical treatment for these diseases.

Since WENDEL[29] reported his epoch-making success in right hepatic lobectomy, successful case of right hepatic lobectomy was reported by HONJO[6] in 1950, which was further followed by reports of total right hepatic lobectomy of WANGENSTEEN[28] in 1951, QUATTELBAUM[20] in 1953 and LORIMER[15] in 1955.

Needless to mention about an uninterrupting endeavour for improvement of surgical technique, marvellous advancement of anesthesiology, development of various antibiotics and progress in pre- and postoperative pertinent care, accumulation of such experiences in extensive hepatic lobectomy largely owes to precious results of investigations on pathophysiologic alteration in organisms brought about by surgical aggression and further on pathophysiology of residual regenerated liver.

Experimental studies on hepatic lobectomy have been widely carried out. In 1883, GLUCK[3] reported that one-third hepatic resection resulted in no recognizable disturbance in rabbits, and PONFICK[19] observed that rabbits could sometimes survive three-fourths hepatic resection. KIDANI[8] successfully carried out 70 per cent hepatic resection in albino rats, and MIKAMI[16] also reported that 85 per cent hepatic resection could be carried out in dogs. According to the experiments of 70 per cent hepatic resection in albino rats by HIGGINS and ANDERSON[5], it was clarified that the residual liver rapidly regenerates after the resection to restore to preoperative size within 2 to 3 weeks. This phenomenon is

accepted to demonstrate prosperous activity of regeneration in the residual liver after extensive hepatic resection.

OKUMURA[18] investigated histologic picture of the residual liver with the lapse of time after 50 per cent hepatic resection in rabbits, and he observed marked degeneration in the residual liver shortly after the resction, which, however, rapidly recovered to completely normal appearance lafter than 3 weeks after surgery.

According to the studies of RIEGELE[21], KUBO[13], SUZUKI[24], KIMURA[10][11] and others on the intrahepatic nerves, the sympathetic, vagus and phrenic nerves enter the liver mainly from the liver hilum along the biliary tract and blood vessels. These nerves form plexus in the interstitial tissue and further enter the hepatic lobules terminating in the net-work.

Recently, HASEBE[4] demonstrated the existence of the nerve which enters the liver from caval opening of the hepatic vein, which is mostly distributed to the hepatic venous system.

Concerning the residual liver after hepatic resection, there is a detailed report of histologic study of OKUMURA as described in the above, and many reports can be seen on its function. However, as far as the author could survey, there is no report of neurohistologic study of the residual liver after hepatic lobectomy.

In the present experiment, 70 per cent hepatic resection was carried out in albino rats, and neurohistologic investigation of the residual liver tissue was made with the lapse of time. The obtained results are reported in the present paper.

II. MATERIALS AND METHODS

A. Materials

Albino rats weighing from 100 to 160 g were used.

B. Methods

1. Preparation of Histologic Section of Regenerated Liver

The liver of albino rats is lobulated into 5 lobes of the left, middle, right, right posterior and caudate lobes. Resection of the left and middle lobes corresponds approximately to 70 per cent, according to HIGGINS and ANDERSON[5] 70. 6 per cent and according to BRUES[6] 68. 4 per cent.

In the present experiment, the hepatic lobectomy was carried out by resection of the left and middle lobes, the vascular pedicles of these lobes being ligated under inhalation anesthesia with ether. Histologic sections were taken from the residual liver tissue 6, 12, 18, 24, 30, 36, 48 hours, 3, 5, 7, 10 days, 2, 3, 4, 5 weeks, 2, 3 and 6 months respectively after hepatic lobectomy.

The residual liver was taken out under inhalation anesthesia with ether. The abdomen was opened, and blood vessels and the bile duct were ligated at the liver hilum and cut. Then, the vena cava inferior was cut near the junction with the hepatic vein, and blood was shed out. The residual liver was quickly extirpated and fixed in a 10 per cent neutral formalin for more than 2 weeks after washing twice with re-distilled water.

2. Staining

For the staining of the histologic section, SUZUKI's modified method[23][30] of BIELSCHOWSKY's silver impregnating method was followed, as briefly described in the below.

1) Slice section

Frozen slice sections of 20 to 40 μ in thickness were made.

2) Preparatory Process

Thirty volumes of formalin and 70 volumes of saturated sodium bicarbonate solution were mixed together and 13 g of hexamethylene-tetramine (Urotropin) was added per 100 cc of the mixture solution. The slice section was immersed approximately for 1 hour in this solution (B. U. F. solution).

3) Rinse

Slice was rinsed with distilled water.

4) Silver impregnation

5) Rinse

Slice was rinsed with formalin solution and distilled water.

6) Immersion in coupled silver solution

7) Reduction

Processed in a 10 per cent solution of tartaric sodium potassium.

8) Rinse

9) Gold Impregnation

10) Slice was included in balsam after rinsed.

III. RESULTS

A. Nerves of Normal Liver

As briefly mentioned in the introduction, the sympathetic, vagus and phrenic three nerves enter the liver, most of which being distributed from the liver hilum along the bile duct and vascular system. The sympathetic and vagus form abdominal plexus, and the branches from the plexus enter the liver. Here, it is generally accepted that the fibres from the left vagus seem to enter the liver directly without passing the abdominal ganglion. The phrenic nerve of the right side enters the liver alone, and forms small diaphragmatic ganglion under the diaphragm. Branches from the ganglion enter the liver through the liver hilum and the others directly through the junction of diaphragmatic peritoneum and hepatic capsule or the hepatic ligament. Within the liver, the nerves mainly run surrounding the blood vessels in the interstitial tissue and are distributed to the periphery in parallel with their longitudinal axis, partly ending in the wall of blood vessels and bile ducts. In the interstitial connective tissue within the liver, the nerves form perivascular nervous plexus close to the vessels, which further form the interlobular nervous plexus communicating with other perivascular plexus and nervous fibres of the vessel wall and bile duct wall. The interlobular nervous plexus further gives fibres to the peripheral area of the hepatic lobules, which finally enter the lobules and fork in a branch-like shape along the capillaries, spreading over the capillaries and hepatic cell cords, to form net-work structure[13].

Concerning the terminal structure of the intrahepatic autonomic nerve, STOEHR[26] called this net-work structure terminal reticulum, and he asserted that the fine fibres of the net-work are sometimes covered with a kind of Leitplasmodium consisted of nervous element, and sometimes distributed as an exposed fibrous net-work without being covered with it. JABONERO[7], however, demonstrated that these fibres are invariably covered with the capsule of Leitplasmodium, and he named these fibres including inner fine fibres Nervoese Syncytium. KIMURA and SAI[10] presumed, as JABONERO had pointed out, that liver cell cord

is surrounded by nervous syncytium, forming so-called "synapse a distance", in which chemical messenger material elaborated from the nervous syncytium conveys impulse to the liver cells.

SUZUKI[24)25)] postulated two types of nervous connection with the liver cells in the hepatic lobules, the one is achieved by 1 or 2 button-like swelling adjoining to biliary capillaries among liver cells and another by interstitial cells through which the impulse is conveyed to the liver cells. The interstitial cells are located closely to the liver cells, covering the surface of the latter with the projection of the former, on the other hand communicating with Leitplasmodium with each other.

From the viewpoint that the interstitial cells are the same cells as have been called SCHWANN's cells and Syncytium of SCHWANN's cells and interstitial cells are essentially identical, KIMURA[11)] put little significance on discriminating particularly these two.

In the normal liver of rats, perivascular and interlobular nervous plexus are observed relatively in abundance in the interstitial connective tissue within the liver, as shown in Fig. 1, 2 and 3 and as the terminal structure in the hepatic lobules, net-work structure of the elementary fibres and interstitial cells scattered among them were observed as in Fig. 4 and 5.

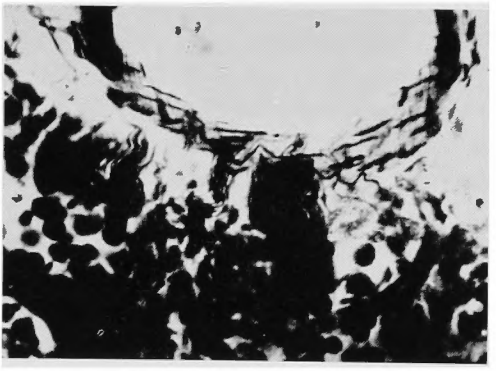

Fig. 1. Nervous Plexus around Blood Vessels in Normal Liver. ×400

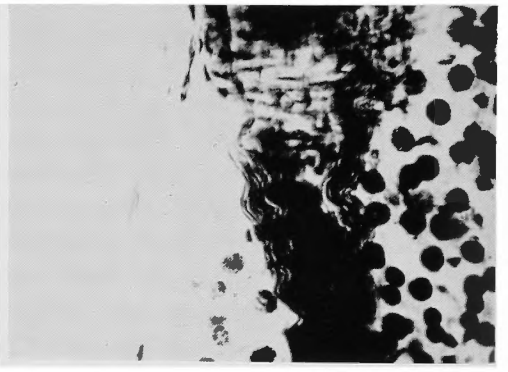

Fig. 2. Nervous Plexus around Blood Vessels in Normal Liver. ×400

Fig. 3. Nervous Plexus in Interlobular Connective Tissue in Normal Liver. ×400

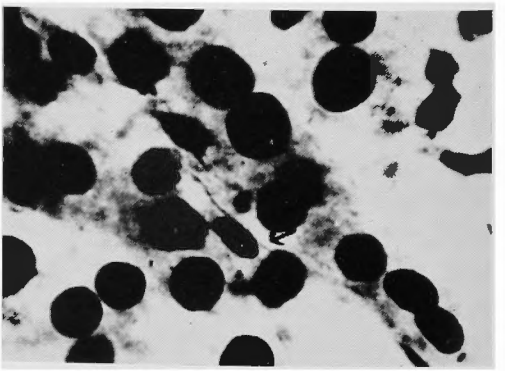

Fig. 4. Elementary Fibres in Terminal Reticulum in Normal Liver. ×1000

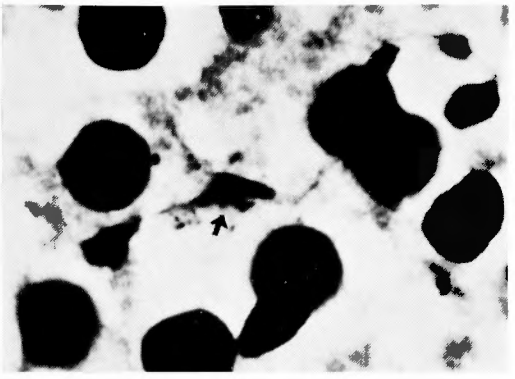

Fig. 5. Interstitial Cells in Normal Liver. ×1500

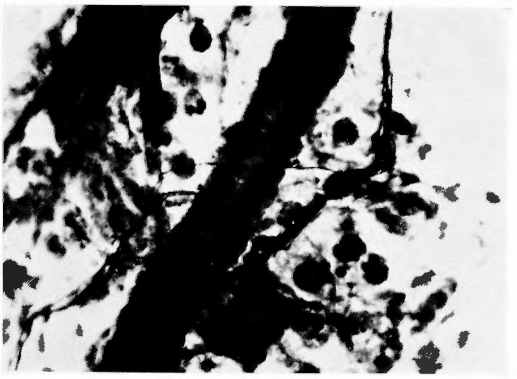

Fig. 6. Nervous Plexus in Interlobular Connective Tissue 18 Hours after Hepatic Lobectomy, Showing no Sign of Degeneration. ×400

B. Nerves of Regenerated Liver

Results of the neurohistologic change in the regenerated liver studied with the lapse of time are summarized in the table.

Table 1 Histologic changes of intrahepatic nerves in parenchyma of residual liver after hepatic resection

Time after Resect.	No. of Rats	Changes of nervous fibres in interlobular connective tissue	Terminal structure	
			Granule formation and fragmentation in elementary fibres in terminal reticulum	Vacuole formation in interstitial cells
6 hours	G 1	−	−	−
	G 2	−	−	−
12 hours	G 3	−	−	−
	G 4	−	−	−
18 hours	K 1	−	−	±
	K 2	−	−	−
	K 3	−	−	±
	K 4	−	−	−
24 hours	F 1	−	+	++
	J 1	−	−	++
	M 1	−	++	+++
	M 2	−	+	++
	M 3	−	±	++
30 hours	L 1	−	−	+
	L 2	−	−	+
	L 3	−	−	−
	L 4	−	−	±
36 hours	N 1	−	−	±
	N 2	−	−	±
	N 3	−	±	±
	N 4	−	−	±

48 hours	I 1	−	−	−
	F 2	−	−	−
3 days	F 3	−	−	−
	H 1	−	−	−
5 days	E 1	−	−	−
	H 2	−	−	−
7 days	D 1	−	−	−
	H 3	−	−	−
10 days	D 2	−	−	−
	H 4	−	−	−
2 weeks	I 2	−	−	−
	A 1	−	−	−
3 weeks	I 3	−	−	−
	A 2	−	−	−
4 weeks	B 1	−	−	−
	B 2	−	−	−
5 weeks	E 2	−	−	−
	Z 1	−	−	−
2 months	D 3	−	−	−
	D 4	−	−	−
3 months	E 3	−	−	−
	E 4	−	−	−
6 months	C 1	−	−	−
	C 2	−	−	−

Six and twelve hours after hepatic lobectomy, the residual liver tissue showed yellowish brown tincture with red spots here and there, macroscopically. As observed by nervous staining, the residual liver at this period showed no significant change in nervous fibres in the GLISSON's sheath and terminal structure in the hepatic lobules.

Eighteen hours after hepatic lobectomy, the liver parenchyma was light yellow, macroscopically, and significant change could not be observed in nerovous fibres in the GLISSON's sheath and terminal elementary fibres, but vacuole formation was observed in cytoplasma of some interstitial cells, as shown in Fig. 6, 7 and 8.

Twenty-four hours after hepatic lobectomy, the liver parenchyma was macroscopically yellow brown with reddish spots. Nervous fibres in the GLISSON's sheath showed no change. However, in some part of terminal reticulum, granular and rosary-like degeneration and fragmentation of the elementary fibres were observed, and remarkable vacuole formation was observed in cytoplasma of interstitial cells, as shown in Fig. 9, 10, 11, 12, 13, 14 and 15. Even in the specimen of the liver with these changes, normal histologic picture could be observed in some other parts of the parenchyma.

Thirty hours after hepatic lobectomy, the liver parenchyma was dark red with yellow

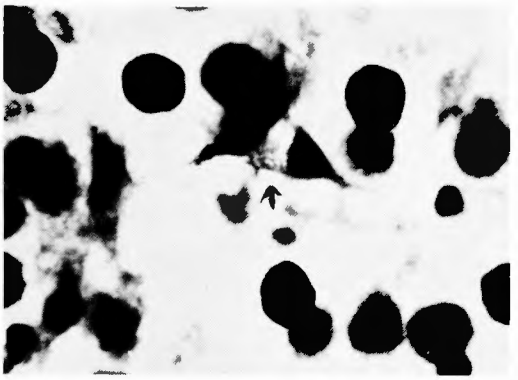

Fig. 7. Vacuole Formation in Interstitial Cells 18 Hours after Hepatic Lobectomy. ×1000

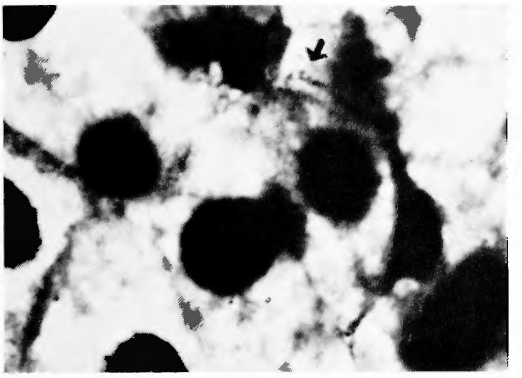

Fig. 8. Vacuole Formation in Interstitial Cells 18 Hours after Hepatic Lobectomy ×1500

Fig. 9. Nervous Plexus around Blood Vessels 24 Hours after Hepatic Lobectomy, Showing no Sign of Degeneration. ×400

Fig. 10. Nervous Plexus in Interlobular Connective Tissue 24 Hours after Hepatic Lobectomy, Showing no Sign of Degeneration. ×400

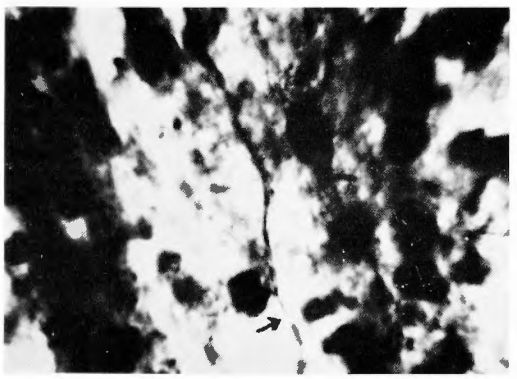

Fig. 11. Segmentation of Nervous Fibres in Marginal Area of Hepatic Lobules 24 Hours after Hepatic Lobectomy. ×1000

Fig. 12. Rosary-Like Degeneration in Nervous Fibres in Hepatic Lobules 24 Hours after Hepatic Lobectomy. ×1500

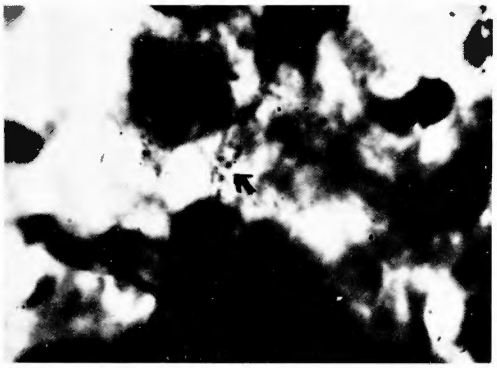

Fig. 13. Fragmentation of Nervous Fibres in Hepatic Lobules 24 Hours after Hepatic Lobectomy. ×1500

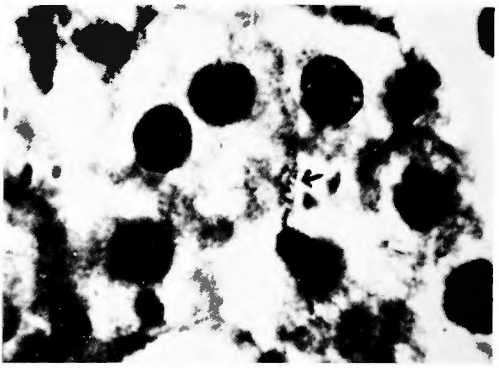

Fig. 14. Fragmentation and Granular Degeneration in Nervous Fibres in Hepatic Lobules 24 Hours after Hepatic Lobectomy. ×1000

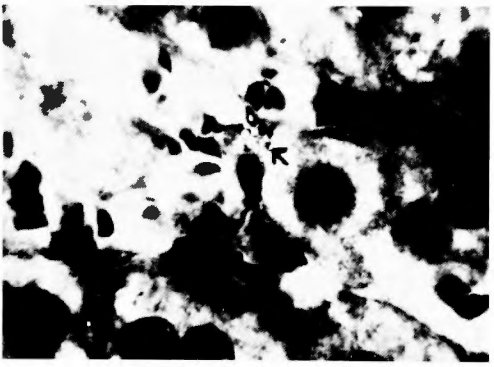

Fig. 15. Marked Vacuole Formation in Interstitial Cells 24 Hours after Hepatic Lobectomy. ×1000

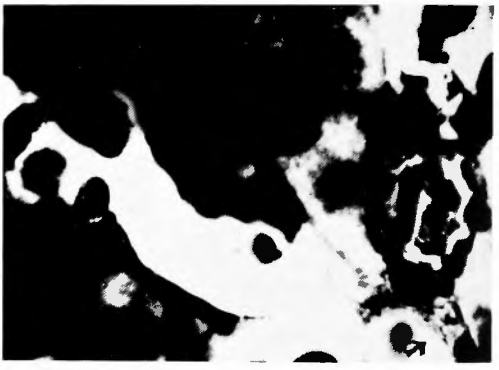

Fig. 16. Vacuole Formation in Interstitial Cells 30 Hours after Hepatic Lobectomy. ×1000

spots in some area. No particular change was observed in nervous fibres in the GLISSON's sheath. Picture of degeneration was not observed also in the elementary fibres of the terminal reticulum. Although vacuole formation was observed in the cytoplasma of interstitial cells, it was not so marked, as shown in Fig. 16 and 17.

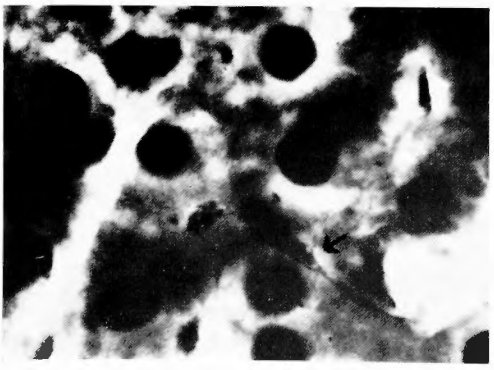

Fig. 17. Vacuole Formation of Slight Degree in Cytoplasma of Interstitial Cells 30 Hours after Hepatic Lobectomy. ×1000

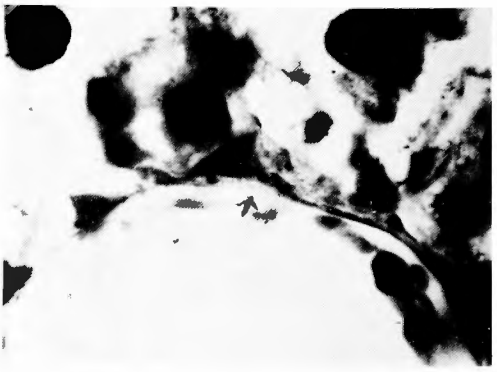

Fig. 18. Vacuole Formation in its Slightest Degree in Cytoplasma of Interstitial Cells 36 Hours after Hepatic Lobectomy. ×1500

Thirty-six hours after hepatic lobectomy, macroscopic appearance of the liver was almost similar to those observed 30 hours after hepatic lobectomy. In the nervous fibres in the GLISSON's sheath, no change was observed. There was a tendency of granular degeneration of the elementary fibres of the terminal reticulum in a small area, and in some part, slight vacuole formation was observed in cytoplasma of interstitial cells, as shown in Fig. 18 and 19.

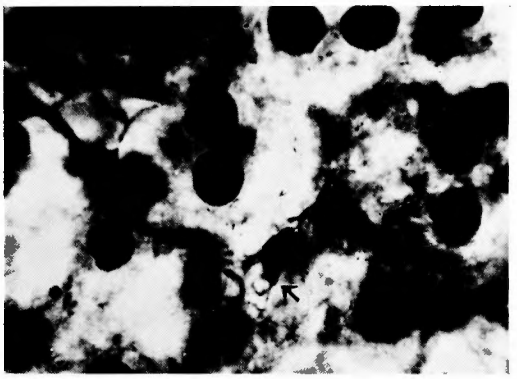

Fig. 19. Vacuole Formation in Interstitial Cells 36 Hours after Hepatic Lobectomy. ×1000

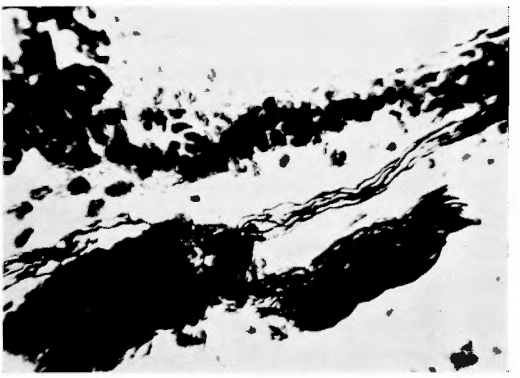

Fig. 20. Nervous Plexus in interlobular Connective Tissue 6 Months after Hepatic Lobectomy. ×400

Forty-eight hours after hepatic lobectomy, the liver showed dark red tincture with yellow spots in some parts. Significant change could be observed neither in the nervous fibres in the GLISSON's sheath nor in the terminal reticulum.

Three days after hepatic lobectomy, macroscopic appearance of the liver was almost normal without significant change in nervous fibres in the GLISSON's sheath and in the terminal reticulum within the hepatic lobules, showing almost normal histologic pattern.

In general, it is considered that liver weight restores to normal within 3 weeks after 70 per cent hepatic lobectomy in rats[5]. As observed in the residual liver later than 3 weeks till 6 months, it was difficult to find a picture of nervous proliferation in the GLISSON's sheath or in the terminal reticulum in the hepatic lobules even at a late period after hepatic lobectomy, as shown in Fig. 20, 21 and 22.

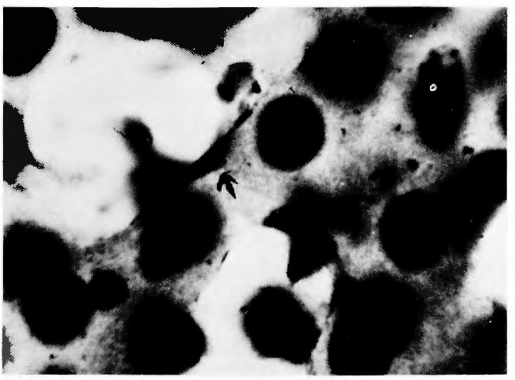

Fig. 21. Interstitial Cells 6 Months after Hepatic Lobectomy. ×1000

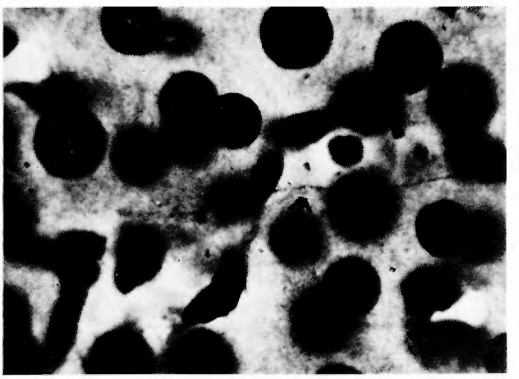

Fig. 22. Nervous Fibres in Hepatic Lobules 6 Months after Hepatic Lobectomy. ×1000

To summarize these findings, neurohistologic finding of the parecnhyma of residual liver after 70 per cent hepatic lobectomy in rats revealed granular and rosary-like degeneration, fragmentation of the elementary fibres in the terminal reticulum and vacuole formation in cytoplasma of interstitial cells only in the early period, and these findings were most marked around 24 hours after hepatic lobectomy. More than 48 hours after hepatic lobectomy, it was difficult to observe these findings, and the findings such as the picture of nervous proliferation could not be observed in the residual liver in a late period after hepatic lobectomy.

On the other hand, no change was observed in the nervous fibres of the perivascular plexus and interlobular plexus even in an early period after hepatic lobectomy, and there was no significant change in these fibres in all the groups of the experimental animals.

IV. DISCUSSION

Concerning the permissible percentage of hepatic lobectomy, GLUCK[3] reported in 1882 that one third resection of the liver was harmless in rabbits, whereas two thirds resection in one stage was invariably lethal within 4 to 5 days. In 1889, PONFICK[19] maintained that the maximum limit of permissible percentage of hepatic resection in animals to be three quarters from his observation, and one quarter hepatic resection resulted only in a temporary disorders in rabbits. He further reported that one half resection of the liver resulted in more or less serious morbid state but it was feasible. His observation confirmed that three quarters resection of the liver was lethal in an early period after the resection, though some animals could manage to survive with improvement of liver function.

From the findings of his histologic study on regeneration of the liver of rats, KIDANI[8] reported in 1952 that 90 per cent hepatic resection was invariably lethal, but animals could survive 65 to 70 per cent hepatic resection, and he maintained that hepatic resection of this extent would be a limit for compensatory function of the residual liver. SOEJIMA[22] insisted that dogs can well survive the aggression of hepatic resection, unless portal blood supply would not be seriously disturbed and he maintained the limit of hepatic resection to be 70 per cent. However, MIKAMI[16] ascertained experimentally that 85 per cent hepatic resection can be feasible in dogs. Comparing the result of 30 per cent hepatic resection with that of 60 per cent, NAKAMURA[17] reported that the larger the amount of the resection, the more prosperous the hypertrophy of the residual liver parenchyma. Since it is considered that the larger the amount of the resection, the more outstanding the changes in the residual liver after hepatic resection, the author of the present experiment carried out a study on the nerve in the residual liver parenchyma after 70 per cent hepatic resection, which is accepted to be a permissible limit of the resection.

As the histologic studies on residual liver after hepatic resection, there is a detailed report of OKUMURA[18] on the results of his 50 per cent hepatic resection in rabbits. Namely, he reported that such findings as intrahepatic congestion, irregular arrangement of hepatic cell cords, irregularity of the size of liver cells, turbid swelling, vacuole formation, necrosis, disappearance of glycogen in liver cells and development of fatty liver could be observed in an early stage of hepatic resection. These changes were, according to his observation, most marked 24 hours after the resection, which were followed by gradual improvement of degenerative change and increase in the figure of indirect mitosis and binucleated cells. He further observed that glycogen increased rapidly from 5 to 7 days after the resection

with the most prosperous hypertrophy, and fat decreased gradually to disappear around 10 days after the resection. In his experiment, histologic appearance improved almost to normal 3 weeks after hepatic resection. MIKAMI[16] also observed the similar findings in dogs and rabbits with 70 per cent hepatic resection and he reported that there were considerably marked changes shortly after the hepatic resection, but 3 months after the resection it was almost impossible to observe increase in lattice and collagen fibres. Histologic study, with the lapse of time in 70 per cent hepatic resection in the present experiment, revealed no change in nervous fibres in the interlobular connective tissue in all groups of the experiment. However, such changes as granular degeneration, rosary-like degeneration, fragmantation in the elementary fibres of the terminal reticulum and vacuole formation in the cytoplasma of the interstitial cells were most outstanding around 24 hours after the hepatic resection. These findings improved thereafter to disappear completely later than 48 hours. Thereafter, no significant change could be observed in the nervous fibres of the terminal reticulum from 3 weeks to 6 months after hepatic resection.

It is assumed that histologic changes of the nervous tissue in the residual liver after hepatic resection showed a similar tendency to those of other hepatic tissues, as compared at the corresponding postoperative period. However, in contrast to the fact that other tissue elements in the residual liver showed marked degeneration all over around 24 hours after the resection, nervous tissue at this period showed the picture of degeneration only in some area and there still remained almost normal findings, suggesting slightness in change in nervous tissue.

Pathologic changes of the nerve are generally called degeneration from the morphologic point of view. Degeneration of the peripheral nerve, however, appear sometimes as a response to stimulation such as injury or inflammation, and sometimes appear as a manifestation of degenerative process after severance of the continuation. The former is called the primary degeneration, and the latter the secondary one. It is difficult to determine only morphologically whether the phenomenon of degeneration means progressive change or regressive one in connection with function of the nerve itself. It is, moreover, difficult to determine whether the degeneration be reversible, unless by some other means.

After severance of the peripheral nerve, destructive process proceeds gradually on the peripheral side. Segmentation and granular degeneration are observed in the nervous fibre and the fibres finally disappear. As the injury of the nerve other than severance above mentioned, injury due to compression and chemical injury can be pointed out. However, it is generally believed that, in compression injury of the nerve, the nerve is not injured by force, but injury of the nerve is mostly due to ischemia caused by circulatory disturbance of the nutritional vessels, which is histologically observed in most cases as swelling of myelin sheath and sometimes associated with the secondary degeneration on the peripheral side of the necrosis, if any. In case of inflammation around the nerve, compression has rather important significance in disturbance of nervous function than chemical irritation. As the cause of the compression, cellular infiltration and following widespread scarring are pointed out. In the autonomic nerve also, changes in the nervous fibres are quite similar[12]. Changes of the nervous tissue in the residual liver parenchyma after hepatic resection might be included in the category of the primary degeneration, since

merely the blood vessels draining into the to-be-resected hepatic lobes are ligated at the liver hilum in the procedure of the resection.

Although the nervous tissue was investigated with the lapse of time in the residual liver parenchyma after hepatic resection, picture of degeneration could not be observed in the nervous fibres in the interlobular connective tissue in all experimental groups. This must be presumably due to the fact that even the sudden change of the condition after hepatic resection would not be adequate as chemical irritation to cause degeneration in the nervous fibres, or such an intense cellular infiltration as to cause compression and degeneration of the nervous fibres do not occur, though there are some report that marked cellular infiltration including spindle cells and small round cells is observed in the GLISSON's sheaths after hepatic resection[18].

In the terminal area of the autonomic nerve, a characteristic net-work structure can be observed. Picture of degeneration in this net-work structure was somewhat different from that of above mentioned nervous fibres. STOEHR[26] called terminal structure of the autonomic nerve terminal reticulum. However, from the fact these reticular fine fibres are always enveloped by SCHWANN's cells, JABONERO[7] insisted to call it NERVEOESE SYNCYTIUM. However, YAMAMOTO[31] demonstrated electron microscopically an obvious existence of the septum between SCHWANN's cells, and from this finding, KIMURA[12] postulated to call the terminal reticulum band of SCHWANN's cells, SCHWANN's band or induction body. The terminal reticulum has been accepted to be the finest net-work structure, but ARAKI[1] reported the existence of electron-microscopically more fine ULTRATERMINAL-NETZ and he maintained that the ULTRATERMINAL-NETZ forms a synapsis with the cells in response. Picture of degeneration appears in the terminal nervous structure reacting against such intense irritations as acute inflammation or acute chemical irritation, and it is recognized by the use of light microscope as granule formation, severance or disappearance of the elementary fibres, turbid swelling or vacuole formation in the SCHWANN's band[9][12]. In the present experiment, outstanding pictures of degeneration such as granule formation and severance in the elementary fibres were observed around 24 hours after hepatic resection, and these changes are interpreted to have appeared as a response to the stimulation of hepatic resection. Furthermore, in this stage after hepatic resection, marked picture of degeneration such as turbid swelling, vacuole formation and karyolexis could be observed histologically in the liver cells[18] Liver function test also revealed the functional disturbance at this stage as demonstrated by markedly increased retention of B. S. P., increase in urinary urobilinogen, decreased synthesis of hippuric acid, increase in blood urea and decreased activity of serum choline esterase[16]. From these findings, it seems logical to consider that above mentioned pictures of degeneration in the nervous elementary fibres are manifestation of degenerative change.

STOEHR[27] maintained that the interstitial cells are peculiar cells and a kind of lower ganglion cells which exist in the site of intersection of SCHWANN's band. KIMURA[12], however, asserted that it might be a transformation of SCHWANN's cells, and ARAKI[1] presumed that the interstitial cells are those which develped in the cell system somewhat embryologically different from SCHWANN's cells, being possessed of intermediate character of nervous cells and SCHWANN's cells. He further considered that these cells are located in the net-work of terminal reticulum with round or irregularly shaped nuclei and releas-

ing fine fibres from the obscure cytoplasma. ARAKI considered the function of these cells to be neurohoromonal and he presumed that in these cells acethylcholine or something like that is produced and these cells adjust the stimulation being located between the related organ and the terminal reticulum. According to ARAKI, the shape of the interstitial cells is different depending upon the feature of the related organ and degenerate or proliferate responding to the stimulation. SUZUKI[25] insisted that the interstitial cells are those of neuroconductive cells, which contact to the related organ with its cytoplasmic protrudings, including nervous elementary fibres within the cytoplasma on the other hand, and each of these cells frequently forms cellular union by cytoplasmic fusion. He, furthermore, maintained that cytoplasmic structure of these cells seems to alter depending on the state of the function, mostly including small fat drops or small fluid vesicles within the cytoplasma, though with much variety in their amount. Although there are various interpretations, opinions of the researchers mostly coincide at least in the respect that the interstitial cells belong to glia system and participate in the transmission of impulse being located between the related organ and terminal reticulum.

In the residual liver parenchyma in rats after hepatic resection, vacuole formation could be observed in the cytoplasma of the interstitial cells exclusively around 24 hours after the resection, whereas such finding could not be observed in the normal liver. Hence, this picture of vacuole formation is interpreted to be a degeneration which appeared as a response to the stimulation of hepatic resection. Since severance of the nervous elementary fibres is observed and decrease in liver function is also demonstrated at this stage, it is presumed that this degenerative pattern also means regressive change.

Physiologic significance of the autonomic nerve which is distributed to the liver is not fully clarified yet. Concerning the influence of the autonomic nerve on metabolism in the liver[14], following views are generally accepted. In sugar metabolism stimulation of the sympathetic nerve enhances decomposition of glycogen (FREUND u. MARSCHAND) and stimulation of the vagus enhances synthesis of glycogen. Catabolism of protein is accelerated by stimulation of the sympathetic nerve and depressed by the stimulation of the parasympatetic nerve (Toenissen), and bile secretion is, as M. EIGER reported, accelerated by the stimulation of the vagus and depressed by the stimulation of the sympathetic nerve. As these reports are based on physiologic or pharmacologic studies, correlation to the morphologic findings is not well discussed, and there remains so much to be solved concerning the mechanism of the intrahepatic autonomic nerve to the liver cells. From the appearance of intrahepatic distribution of the nerve, however, there is no doubt in assuming the regulatory role of the autonomic nerve to the liver cells. Abundant nervous distribution is observed in the intrahepatic blood vessels, and, according to KUBO[13], the nervous fibres are most abundant in the adventitia running longitudinally, running circumferentially in the media, reaching the intima under the proper membrane of the endothelial layer and further among the endothelial cells.

Within the hepatic lobules, capillaries are surrounded together with the hepatic cell cord by the terminal reticulum. Accordingly, it is assumed that the intrahepatic vascular system receives abundant distribution of the autonomic nerve. The sympathetic nerve participates in the contraction of the intrahepatic blood vessels, and the vagus is antagonistic to the sympathetic nerve. However, it is presumed that various factors stimulate the

vasomotoric nerve, influencing on the intrahepatic blood flow and secondarily participating in the secretory mechanism of the hepatic cells. It is, furthermore, presumable from the view-point of innervation of the autonomic nerve to the hepatic cells and nervous participation in the intrahepatic blood flow, that the autonomic nerve has large innfluence on the metabolism of the liver. In 70 per cent hepatic resection in dogs and rabbits, as reported by MIKAMI[16] liver function test revealed marked decrease in the function around 24 hour after the resection, which improved gradually, blood sugar, lactose, pyruvic acid, amino acid, ammonia and urea in blood and the result of galactose loading restoring to the preoperative level from 1 to 2 weeks after the resection. In his experiments, liver function improved around 2 weeks after the resection as determined by B. S. P. retention test, urobilinogen content and hippuric acid test, and it was suggested that the hepatic regeneration was preceded by the improvement of metabolic function.

In the present experiment, granule formation and fragmentation were observed in the nervous elementary fibres of the terminal reticulum around 24 hours after the resection of the liver, and the degenerative picture could not be observed later than 48 hours after the resection. This finding is interpreted to support neurologically functional recovery of the liver, considering from the relationship between liver function and the autonomic nerve, although it should be taken into account that degenerative picture of the liver cells is replaced by the picture of repair toward 48 hours after the hepatic resection.

Degenerative phenomenon of the nerve in the terminal reticulum of the ending of the autonomic nerve is replaced by the regeneration of the newly produced fibres through the BUENGNER's band formed by the proliferation of SCHWANN's cells being supported by originally possessed prosperous regenerative activity, when the cause of the degeneration is removed or the cause turns out to have only a little effect[1]. Quantitative study of hepatic regeneration in rats with 70. 6 per cent hepatic resection made by HIGGINS and ANDERSON[5] revealed that the residual liver parenchyma was 45. 3 per cent of the preoperative volume 24 hours after the resection and 53. 5 per cent 48 hours after the resection, and the histologic study also revealed mitotic figures of the liver cells in the marginal area of the hepatic lobules 24 hours after the resection. Thus, it is widely accepted that hepatic regeneration occurs vigorously from 24 hours after the resection. However, little is disclosed concerning the detailed process of the regeneration, some insisting that the regeneration is completed by the enlargement of the hepatic lobules themselves and others insisting that it is completed by the formation of the new lobules, and definitive opinion is not established yet[18]. On the other hand, ARAKI[1] observed the existence of abundant terminal reticulum containing nervous cells in the capillary, and he investigated regeneration of the nerve in the capillary at the formation of the granulation tissue by making a round window in the ear-lobe of rabbits. In his experiments, he observed that the capillaries first regenerated and a little later the nerves regenerated. He further observed that the nervous distribution in the butter-yellow hepatic adenoma was almost similar to that of the normal liver, and this relationship was well preserved even after the adenoma had developed to carcinoma, without the evidence of injury in the nervous elementary fibres caused by cancer cells.

In the present experiment, it was impossible to demonstrate how the nerve regenerates in the regenerated liver parenchyma. It was also difficult to clarify whether the above

mentioned degenerative changes such as granule formation and fragmentation in the nervous elementary fibres observed around 24 hours after the resection be the reversible ones or not. However, judging from the finding that nervous distribution was almost similar to that of the normal liver later than 48 hours after the hepatic resection, it is presumed that the appearances of the nervous distribution after hepatectomy become almost similar to those of the normal liver by progressive regeneration of the nervous elementary fibres being associated with the SCHWANN's band together with the regeneration of the capillaries in the regenerated liver, along with the decrease in the effect of stimulation of hepatic resection on the nervous tissue and onset of the regeneration of the liver cells.

V. SUMMARY

In albino rats, 70 per cent hepatic resection was carried out and the residual liver parenchyma was taken with the lapse of time, which was neurohistologically studied by the SUZUKI's modified method of BIELSCHOWSKY's silver impregnation. The obtained results are summarized as follows:

1) In the early stage after hepatic resection, granular degeneration and fragmantation of the elementary fibres in the terminal reticulum, which is understood to be the intrahepatic ending of the autonomic nerve, and vacuole formation in the cytoplasma of the interstitial cells were observed. These changes were most outstanding around 24 hours after the resection, degree of which gradually improving thereafter, and degenerative changes could not be observed later than 48 hours after the resection.

2) Picture of degeneration could not be observed even in the early stage after the resection in the nervous fibres in the interlobular connective tissue.

3) Even 3 to 6 months after the resection, picture of proliferation could not be observed in the nervous fibres in the interlobular connective tissue as well as in the terminal reticulum.

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(*in Japanese)

和文抄録

再生肝の神経

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従来肝切除に関する実験的研究は多く，奥村は家兎の50%肝切除を行ない経時的に残存肝の組織像を追究し，残存肝には術後間もなく著明な退行変性像の出現をみるが，速やかに恢復し，3週以後においては全く正常化することを報告している．また三上は犬あるいは家兎における70%肝切除後の肝機能検査で，術後24時間内外に著明な肝機能低下を来すが，次第に恢復に向い，2週間前後で術前値に戻ることを認めている．

肝切除後の残存肝の変化は，切除量の大なる程著明と考えられるので，著者は大黒鼠を使用し，その切除許容量と考えられる70%肝切除を行ない，残存肝を経時的に採取し，Bielschowsky 氏鍍銀法—鈴木氏変法にて神経組織学的検索を行ない，次の結果を得た．

1) 肝切除後早期に肝内自律神経終末である終網原線維の顆粒状変性，断裂化および介在細胞の形質内空胞形成を認める．その最も著しい時期は，肝切除24時間前後で，以後次第に病変の程度を減じ，48時間以後のものでは変性像を認めない．

2) 肝内小葉間結合織を走る神経線維には，術後早期期においても変性像を認めなかつた．

3) 肝切除後3～6ヵ月後においても，肝小葉間結合織の神経線維にも，終末構造である終網にも増殖像は認められなかつた．