An Experimental Study on Bile Excretion in Regenerated Liver

By

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CONTENT

I. INTRODUCTION

Since GLUCK[1] reported in 1882 that resection of one-third of the liver can be safely carried out, many experimental studies have been accumulated. CECCHERELLE[2], in 1884, and PONFICK[3], in 1889 reported that some of the experimental animals survived the excision of three-fourths of the liver, which was followed by the likewise results of MEISTER[4], in 1894, FLÖCK[5], in 1895 and KAHN[6], in 1897. BOLLMAN and MANN[7] observed in 1936 that the liver maintained normal function even in dogs with four-fifths hepatic excision and with ECK fistula to prevent regeneration of the liver. They also asserted that excretion of bile is hardly affected by extensive resection of the liver.

On the other hand in our country, KOBAYASHI[8] and HIRANO[9], in 1943, KIDANI[10], in 1952, SOEJIMA[11], in 1954 and MIKAMI[12], in recent years respectively reported that the liver exerts normal function overcoming surgical aggression after extensive resection of the liver. When the liver is thus widely excised, the life of organism still remains safe owing to functional reserve and regenerative capacity of this organ, as has been clarified by pathophysiological studies. According to MIKAMI[12], 20 per cent hepatic resection in normal dogs resulted in liver failure of a slight degree as examined by relatively subtle

* The gist of the present paper was reported at 51st Annual Meeting of Japanese Society of the Diseases of Digestive Organs.

examinations as activity of alkaline phosphatase, B. S. P. retention test and thymol turbidity test, which, however improves within a week or so. The deta of these examinations fluctuate largely after 70 per cent hepatic resection, revealing marked disturbance of all the functions of the liver until 36 hours after the resection. However, regeneration of the liver could be observed already at this period, which reached the normal level in quantity and quality with the lapse of 4 weeks to exert nomal function. Here, among various liver functions metabolic function improves prior to regeneration of this organ, while, general other function recovers slightly later.

As has been surveyed, there have been carried out numerous studies on pathophysiology of hepatic resection. However, concerning functional alteration during the process of regeneration, although one could roughly estimate the disturbed function in the early period by routine examinations, it was only vaguely known from these examinations that the function had recovered to nomal.

In the present experiment, investigations were carried out on hepatic bile excreted from the liver with the lapse of time after hepatic resection in order to explore more exactly the functional alteration of the regenerative liver.

II. MATERIALS AND METHODS

1. Materials

Adult mongrel dogs weighing about 10 kg were used in the experiment regardless of sex, in healthy condition.

Since excretion of bile is closely associated with quality and quantity of diet and with its digestion and absorption, diet was constantly given from 9.00 to 10.00 a. m. The diet was constantly consisted of boiled rice of 400 g, boiled fish of 70 g and 20 cc of shoyu (a seasoning sauce), which were mixed together with 200 cc of water. This diet contained nutritionally 41 g of protein, 7 g of fat and 307 g of carbohydrate with 1450 Cal. in total. Attention was paid so that the animals finish entire amount of the diet as possible.

2. Methods

For the collection of hepatic bile, dogs were anesthetized with an injection of 2.5 per cent isozol solution of 0.5 cc/kg body weight from the femoral vein in the state of fasting for 24 hours, and during the experiment 1 to 2 cc of isozol solution was appropriately injected intravenously in order to maintain a constant depth of anesthesia, condition of respiration mainly being taken as an indicator. Dogs were fixed in the spine position, and the abdomen was opened by an upper median incision. The gall-bladder was first extirpated to prevent intermingling with cystic bile. Then, a small incision of 1 cm in length was laid longitudinally on the duodenum and the papilla of Vater was groped for, from which a No. 30 gauge polyethylene tube was inserted to the choledochus. The tube was introduced extracorporeally through the duodenal incision and incisional wound of the abdominal wall. Incisional wound of the duodenum was closed with all layer suture remaining the tube in situ, and the abdominal wall was also closed. Bile flowed out from the tube was collected. Since it was assumed that there existed a possibility of intermigling of cystic bile with the bile thus collected during initial 5 minutes, it was discarded, and hepatic bile was collected thereafter precisely for 1 hour. When the bile excretion was

Illustration of Experiment

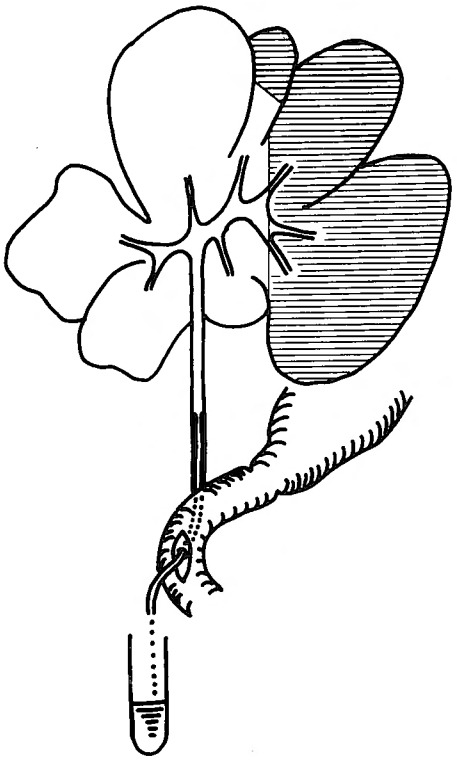


Fig. 1 Following cholecystectomy, the left superior and inferior lobes, a part of the middle, quadrate and caudate lobes were resected. Bile was collected from a tube inserted transduodenally into the bile duct.

small in amount, however, it was collected for 2 hours.

After the collection of hepatic bile prior to hepatic resection, the abdomen was again opened to remove the polyethylene tube inserted into the choledochus through the duodenum, and incisional hole of the duodenum was entirely and tightly closed.

Then, the left superior, left inferior, middle, quadrate lobes and a part of the caudate lobe of the liver were resected under mass ligature. Weight of the resected liver corresponded approximately to 50 per cent of the entire liver weight[11)13)~16)]. The abdomen was closed primarily after penicillin was put in.

During the operation, no other drug than isozol was injected (Fig 1).

In the similar manner as described in the above, hepatic bile was collected for 1 to 2 hours through the tube inserted transduodenally into the choledochus, 2 days, 1 week, 2 weeks, 3 weeks, 1 month, 2 months and 3 months respectively after hepatic resection. The final collection of hepatic bile in this series of the examination, 3 months after hepatic resection, was carried out through a tube No. 30 gauge directly inserted into the choledochus.

Blood was taken from the femoral vein immediately before the collection of bile at each period, which was subjected to various examinations, and B. S. P. retention test was performed on the previous day of the collection of bile.

3. Methods of Determination

a. Serum Protein Level

Serum protein level was determined by Atago Refractometer for serum protein[17)].

b. B. S. P. Retention Test

Five per cent solution of bromsulfalein was injected into the femoral vein in a proportion of 0.1 cc/kg body weight. Blood was taken from the femoral vein on another side 15 minutes later, and used for colorimetry[17)]

c. Serum Bilirubin Level

Serum bilirubin level was determined colorimetrically following the method of MEULENGRACHT for determination of icterus index[17)].

d. Bilirubin Level in Hepatic Bile

Hepatic bile was accurately diluted to 200 times and bilirubin level was determined

by colorimetry according to EVELYN-MALLOY's quantitative method of determination using COLEMAN's spectrocolorimeter[17][18].

e. Phospholipid Level

Lipid-P both in serum and in hepatic bile was colorimetrically determined with amino-naphthol-sulfonic acid method, and 25 times of the obtained value was taken as phospholipid level[19].

f. Serum Cholesterol Level

Serum cholesterol level was determined colorimetrically by ZAK's extraction method based on KILLIANI's reaction[17]. Cholesterol-ester ratio was calculated from the proportion between total cholesterol level and esterified cholesterol.

g. Total Cholesterol Level in Hepatic Bile

Hepatic bile was hydrolysed, which was then extracted with petroleum ether. Total cholesterol level was colorimetrically determined by ABELL's modified mothod[20] based on KILLIANI's reaction.

h. Total Bile Acid Level in Hepatic Bile

Using Vanillin phosphoric acid method of MURAKAMI[21], trihydroxycholanic acid and dihydroxycholanic acid were respectively determined by colorimetry and sum of these two was looked upon as total bile acid.

III. RESULTS

1. Body Weight

As shown in Fig. 2 and Tab. 3, preoperative body weight was 13.0 kg in the maximum, 7.5 kg in the minimum and 9.6 kg on the average. It gradually decreased after the resection of the liver to reach the minumum of 8.6 kg, on the average, 1 month after surgery, being 1 kg less compared with preoperative average body weight. Body weight showed gradual increase thereafter restoring to preoperative one 2 months after hepatic resection.

2. Serum Protein Level

As represented in Fig. 3, Tab. 1 and Tab. 4, preoperative maximum value was 7.5 g/dl, preoperative minimum value 5.6 g/dl and average one 6.6 g/dl. After hepatic resection, serum protein level gradually decreased reaching the minimum value of 6.1 g/dl around 2 weeks later, which showed an increase thereafter restoring to preoperative level in almost all cases from 3 weeks to 1 month after surgery. It was maintained in the preoperative level as determined 2 and 3 month after surgery, respectively.

3. B. S. P. Retention Test

As shown in Fig. 4, Tab. 1 and Tab. 5, preoperative maximum value was 2.5 per cent, minimum value being 0 per cent and average value being 1.7 per cent. Two days after hepatic resection, the maximum value was 15.0 per cent, the minimum value was 7.5 per cent, elimination being retarded, and average value was 10.5 per cent. One week after surgery, the average value returned to 3.8 per cent approaching to nomal level, which showed a slight fluctuation within the normal range 2 weeks after surgery.

4. Serum Bilirubin Level (Icterus Index)

As shown in Fig. 5, Tab. 1 and Tab. 6, preoperative maximum value was 3.5 units,

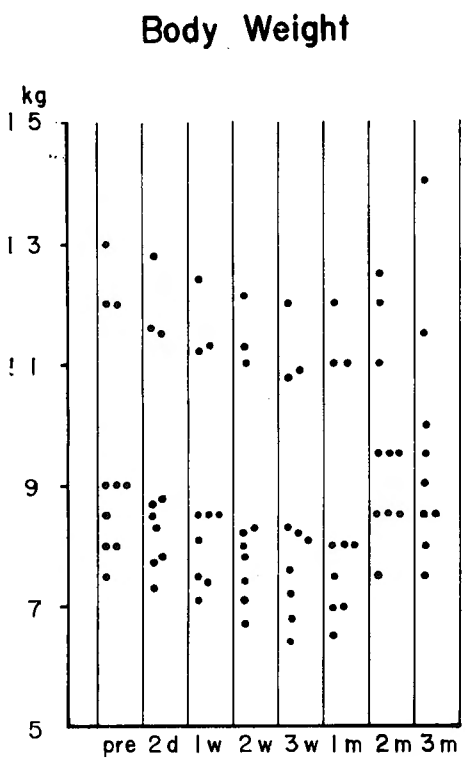


Fig. 2 Body weight temporarily decreased after hepatic resection, and restored to preoperative level 2 months after surgery.

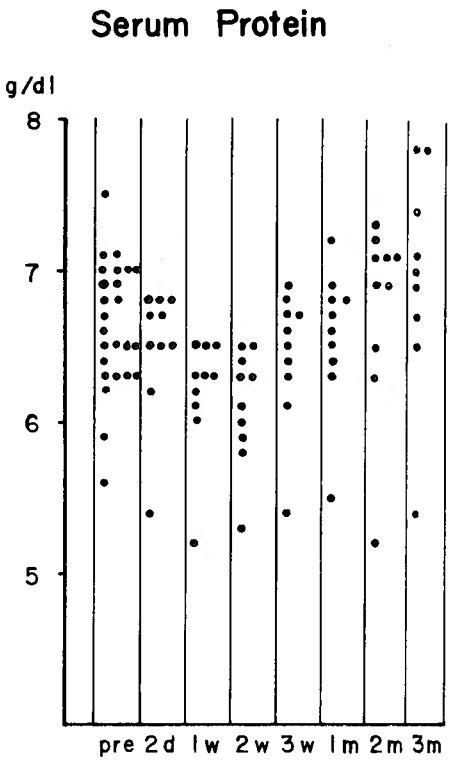


Fig. 3 Serum protein level decreased gradually after surgery to reach the minimum 2 weeks after surgery, which restored to preoperative level 1 month after surgery.

Tab. 3 Body Weight (kg)

Dog No. \ Time after Surgery	pre	2d	1w	2w	3w	1m	2m	3m
16	12.0	11.6	11.0	11.3	10.8	11.0	12.0	
2	7.5	7.3	7.4	6.7	6.9	6.5	7.5	7.5
19	8.0	7.7	7.5	7.5	7.2	7.0	8.5	8.0
28	8.0	7.8	7.1	7.1	6.8	7.0	8.5	8.5
5	9.0	8.7	8.5	8.3	8.4	8.0	9.5	9.5
18	9.0	8.8	8.5	8.0	8.2	8.0	9.5	9.0
9	9.0	8.5	8.5	8.3	8.1	8.0	9.5	10.0
31	12.0	11.5	11.3	11.3	10.9	11.0	11.0	14.0
34	13.0	12.8	12.4	12.1	12.0	12.0	12.5	11.5
23	8.5	8.3	8.1	7.8	7.6	7.5	8.5	8.5
Mean	9.6	9.3	9.1	8.8	8.7	8.6	9.7	9.6

Tab. 1 Preoperative Values in Serum

Dog No.	Serum Protein g/dl	B•S•P %	Icterus Index units	Phospholipid mg/dl	Total Cholesterol mg/dl	Cholesterol-Ester Ratio %
16	7.0	2.5	2.0	175	128	73.5
2	6.5	2.5	2.5	167	137	75.1
19	6.9	0	2.0	161	141	72.2
28	5.6	2.5	2.0	185	132	74.3
5	7.1	0	2.0	196	143	70.8
18	7.0	2.5	2.5	155	123	78.1
9	6.8	2.5	2.0	198	159	77.1
31	6.5	0	2.5	159	148	75.2
34	6.2	2.5	2.5	161	126	72.2
23	6.9	0	2.0	165	150	77.3
17	6.3	2.5	2.5	176	149	69.8
36	7.1	2.5	2.0	201	152	72.5
35	6.6	2.5	2.5	236	146	79.5
38	7.0	2.5	2.5	214	170	74.7
39	7.0	2.5	2.0	184	170	79.4
40	6.5	0	2.5	186	164	75.0
41	6.8	2.5	2.5	218	171	76.0
11	6.3	2.5	2.0	191	120	68.3
45	6.3	2.5	2.0	123	160	73.3
46	6.5	0	2.0	185	182	76.2
47	7.5	0	2.5	206	174	73.6
48	6.7	2.5	2.0	132	138	68.2
49	5.9	2.5	2.5	173	124	65.5
50	6.3	0	2.0	188	104	67.3
51	6.4	2.5	2.0	156	116	72.4
Mean	6.6	1.7	2.2	180	145	73.5

Tab. 4 Serum Protein (g/dl)

Time after Surgery / Dog No.	pre	2d	1w	2w	3w	1m	2m	3m
16	7.0	6.7	6.3	6.3	6.6	6.6	6.9	
2	6.5	6.5	6.3	6.3	6.1	6.4	7.1	7.8
19	6.9	6.7	6.3	6.1	6.8	7.2	7.2	7.8
28	5.6	5.4	5.2	5.3	5.4	5.5	5.2	5.4
5	7.1	6.8	6.5	6.5	6.7	6.7	7.3	7.4
18	7.0	6.8	6.5	6.4	6.9	6.8	7.1	6.9
9	6.8	6.5	6.2	6.0	6.5	6.9	7.1	7.1
31	6.5	6.2	6.1	5.8	6.3	6.5	6.9	6.7
34	6.2	6.5	6.0	5.9	6.4	6.3	6.3	7.0
23	6.9	6.8	6.5	6.5	6.7	6.8	6.5	6.5
Mean	6.6	6.5	6.2	6.1	6.4	6.6	6.8	7.0

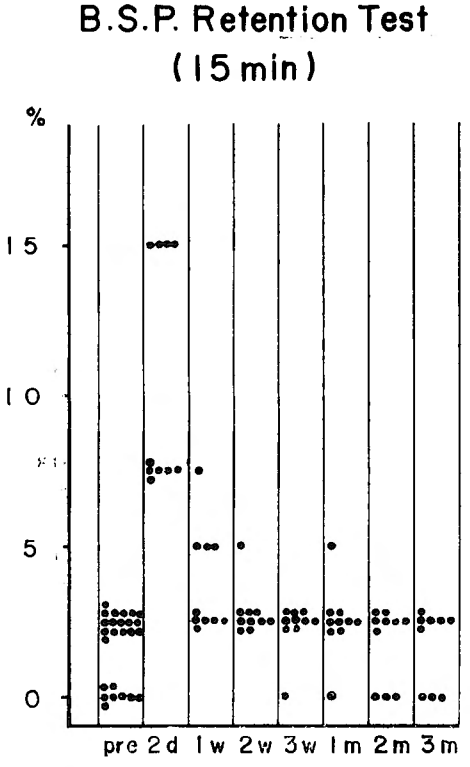


Fig. 4 Rate of B. S. P. retention increased immediately after surgery, which, however, restored to normal 2 weeks after surgery.

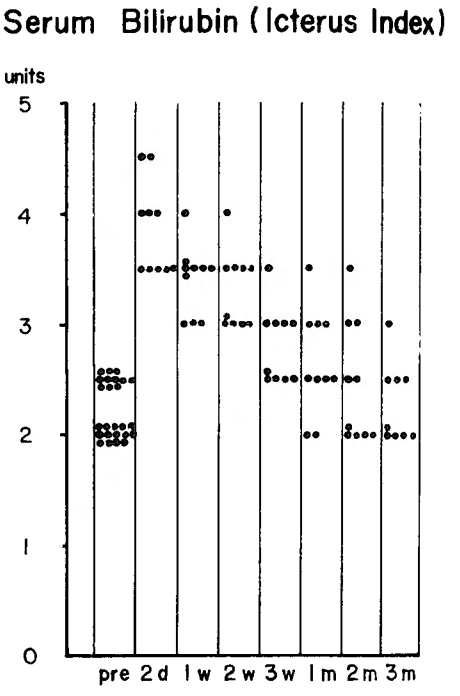


Fig. 5 Serum bilirubin level (icterus index) showed temporary increase immediately after surgery, which retruned to normal shortly.

Tab. 5 B. S. P. Retention Test (15 min.) (%)

Time after Surgery / Dog No.	pre	2d	1w	2w	3w	1m	2m	3m
16	2.5	15.0	2.5	2.5	2.5	2.5	2.5	
2	2.5	7.5	2.5	2.5	2.5	2.5	2.5	2.5
19	0	7.5	5.0	5.0	2.5	2.5	0	0
28	2.5	15.0	7.5	2.5	2.5	2.5	2.5	2.5
5	0	7.5	2.5	2.5	2.5	2.5	2.5	2.5
18	2.5	15.0	5.0	2.5	2.5	2.5	2.5	2.5
9	2.5	7.5	2.5	2.5	2.5	0	0	0
31	0	7.5	5.0	2.5	2.5	5.0	2.5	2.5
34	2.5	15.0	2.5	2.5	2.5	2.5	2.5	2.5
23	0	7.5	2.5	2.5	0	2.5	0	0
Mean	1.7	16.5	3.8	2.8	2.3	2.5	1.8	1.7

Tab. 6 Serum Bilirubin (Icterus Index)

Time after Surgery / Dog No.	pre	2d	1w	2w	3w	1m	2m	3m
16	2.0	4.0	3.5	3.5	3.0	2.0	2.0	
2	2.5	3.5	3.5	3.0	3.0	3.0	3.0	3.0
19	2.0	4.0	3.5	3.0	3.0	2.5	2.0	2.0
28	2.0	3.5	3.0	3.5	2.5	3.0	2.0	2.0
5	2.0	4.0	3.5	3.5	2.5	2.0	2.0	2.0
18	2.5	4.5	4.0	4.0	3.0	3.0	3.0	2.5
9	2.0	3.5	3.0	3.0	2.5	2.5	2.5	2.5
31	2.5	3.5	3.5	3.0	2.5	2.5	2.5	2.5
34	2.5	4.5	3.5	3.5	3.5	3.5	3.5	2.0
23	2.0	3.5	3.0	3.0	2.5	2.5	2.0	2.0
Mean	2.2	3.9	3.4	3.3	2.8	2.7	2.5	2.3

the minimum value was 2.0 units and average value was 2.2 units. Two days after hepatic resection, it being increased, the maximum value was 4.5 units and the minimum value was 3.5 units, average value being 3.9 units. However, with this degree of increase in serum bilirubin, manifestation of jaundice could not be observed at all, out-look of the animals being completely normal. Serum bilirubin decreased gradually thereafter showing fluctuation within the normal range.

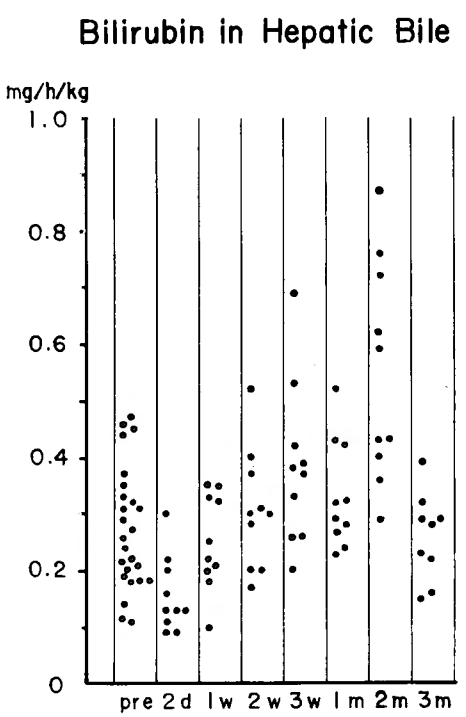


Fig. 6 Bilirubin content in hepatic bile decreased after surgery, and it increased markedly 2 months after surgery, which restored to preoperative level 3 months after surgery.

5. Bilirubin Level in Hepatic Bile

As in Fig. 6, Tab. 2 and Tab. 7, preoperative maximum value was 47 mg/h/kg body weight, the minimum value was 0.11 mg/h/kg body whight and average value was 0.27 mg/h/kg body weight. Two days after hepatic resection, the maximum value was 0.30 mg/h/kg body weight, the minimum value was 0.09 mg/h/kg body weight, showing decrease, and average value was 0.15 mg/h/kg body weight. The average value was thereafter 0.25 mg/h/kg body weight 1 week after surgery, 0.30 mg/h/kg body weight 2 weeks after surgery, 0.38 mg/h/kg body weight 3 weeks after surgery, 0.33 mg/h/kg body weight 1 month after surgery, thus gradually increasing, and 2 months after surgery the maximum value was 0.88 mg/h/kg body weight, the minimum value was 0.29 mg/h/kg body weight and average value was 0.55 mg/h/kg body weight, showing

Tab. 2 Preoperative Values in Hepatic Bile

Dog No.	Amount of Excreted Bile cc/h/kg	Bilirubin mg/h/kg	Phospholipid mg/h/kg	Total Cholesterol mg/h/kg	Total Bile Acid mg/h/kg
16	0.15	0.215	0.7	0.044	4.1
2	0.53	0.201	1.6	0.096	7.5
19	0.19	0.115	1.7	0.089	2.5
28	0.14	0.111	1.7	0.044	2.3
5	0.45	0.332	2.9	0.126	8.5
18	0.21	0.308	1.0	0.097	3.5
9	0.22	0.258	0.9	0.033	2.5
31	0.29	0.354	2.0	0.053	5.8
34	0.46	0.268	1.5	0.094	9.1
23	0.35	0.367	2.3	0.098	4.7
17	0.33	0.456	1.8	0.037	6.0
36	0.25	0.216	3.4	0.065	4.8
35	0.41	0.294	5.2	0.077	11.3
38	0.34	0.321	3.4	0.068	7.6
39	0.57	0.187	5.1	0.093	10.9
40	0.16	0.179	2.2	0.023	5.8
41	0.28	0.241	2.7	0.137	4.6
44	0.10	0.142	0.8	0.054	2.2
45	0.29	0.182	3.6	0.038	5.3
46	0.42	0.438	5.8	0.118	2.9
47	0.43	0.451	2.6	0.103	5.5
48	0.52	0.474	1.0	0.058	10.1
49	0.26	0.209	2.0	0.020	3.3
50	0.32	0.314	2.3	0.066	3.8
51	0.28	0.180	1.7	0.125	10.8
Mean	0.32	0.273	2.8	0.074	5.8

Tab. 7 Bilirubin in Hepatic Bile ($\times 10^{-2}$ mg/h/kg)

Dog No. \ Time after Surgery	pre	2 d	1 w	2 w	3 w	1 m	2 m	3 m
16	21.5	15.8	25.3	30.4	38.4	22.5	43.5	
2	20.4	12.5	22.1	19.8	25.5	29.1	72.0	28.8
19	11.5	8.9	10.1	16.9	20.3	21.0	87.6	15.4
28	11.1	9.2	18.2	19.5	25.8	27.4	29.4	15.6
5	33.2	29.8	32.5	52.3	69.2	27.5	40.4	39.4
18	30.8	20.1	34.8	30.6	42.3	51.5	62.0	32.3
9	25.8	11.1	20.7	27.5	39.2	43.3	43.3	23.2
31	35.4	12.6	19.8	30.1	32.7	31.5	35.5	27.9
34	26.8	12.5	35.1	37.6	52.5	42.3	59.4	28.7
23	36.7	21.5	31.8	39.5	36.7	31.7	76.2	22.3
Mean	27.3	15.4	25.1	30.4	38.3	33.1	54.9	26.0

markedly increased value twice as much compared preoperative one. The value tended to decrease again to return to normal level 3 months after surgery, showing average value of 0.26 mg/h/kg body weight.

6. Amount of Excreted Hepatic Bile

As in Fig. 7, Tab. 2 and Tab. 8, preoperative maximum value was 0.57 cc/h/kg body weight, the minimum value was 0.10 cc/h/kg body weight and average value was 0.32 cc/h/kg body weight. Two days after hepatic resection, the maximum value was 0.41 cc/h/kg body weight, the minimum value was 0.05 cc/h/kg body weight and average value was 0.18 cc/h/kg body weight, showing remarkable decrease. The average value was thereafter 0.27 cc/h/kg body weight 1 week after surgery, 0.37 cc/h/kg body weight 2 weeks after surgery, 0.45 cc/h/kg body weight 3 weeks after surgery and 0.49 cc/h/kg body weight 1 month after surgery, showing gradual increase. Two months after surgery, the maximum value was 0.88 cc/h/kg body weight, the minimum value was 0.45 cc/h/kg body whight and average value was 0.67 cc/h/kg body weight, reaching 2.1 times level of preoperative average value. The value again deceased thereafter to restore to the normal level 3 months after surgery, the average value being 0.31 cc/h/kg body weight.

7. Serum Phospholipid Level

As represented in Fig. 8, Tab. 1 and Tab. 9, preoperative maximum value was 236 mg/dl, the minimum value was 123 mg/dl and average value was 180 mg/dl. Two days after surgery, the maximum value was 327 mg/dl, the minimum value was 258 mg/dl and average value was 288 mg/dl, revealing remarkable increase. The average value was thereafter 224 mg/dl 1 week after surgery, 197 mg/dl 2 weeks after surgery, 180 mg/dl 3 weeks after surgery, restoring to nomal at this period. The value slightly fluctuated within the normal level 1, 2 and 3 months after surgery, respectively.

8. Phospholipid Level in Hepatic Bile

As represented in Fig. 9, Tab. 2 and Tab. 10, preoperative maximum value was 5.8 mg/h/kg body weight, the minimum value was 0.7 mg/h/kg body weight and average value was 2.8 mg/h/kg body weight. Two days after hepatic resection, the maximum value was 2.1 mg/h/kg body weight, the minimum value was 0.2 mg/h/kg body weight and average value was 0.9 mg/h/kg body whight, demonstrating marked decrease. The average value thereafter showed gradual increase as 1.7 mg/h/kg body weight, 1 week after surgery, 2.8 mg/h/kg body weight 2 weeks after surgery, 3.3 mg/h/kg body weight 3 weeks after surgery and 3.9 mg/h/kg body weight 1 month after surgery. Two months after surgery, the maximum value was 10.0 mg/h/kg, the minimum value was 4.3 mg/h/kg body weight and average value was 6.3 mg/h/kg body weight, showing increase of 2.3 times of preoperative value. The value decreased again thereafter returning to normal, showing the average value of 3.2 mg/h/kg body weight 3 months after surgery.

9. Total Cholesterol Level in Serum

As in Fig. 10, Tab. 1 and Tab. 11, preoperative maximum value was 182 mg/dl, the minimum value was 104 mg/dl and average value was 145 mg/dl. Two days after surgery, the maximum value was 217 mg/dl, the minimum value was 182 mg/dl and average value was 196 mg/dl, showing remarkable increase. The average value thereafter was 182 mg/dl 1 week after surgery, 149 mg/dl 2 weeks after surgery, 147 mg/dl 3 weeks

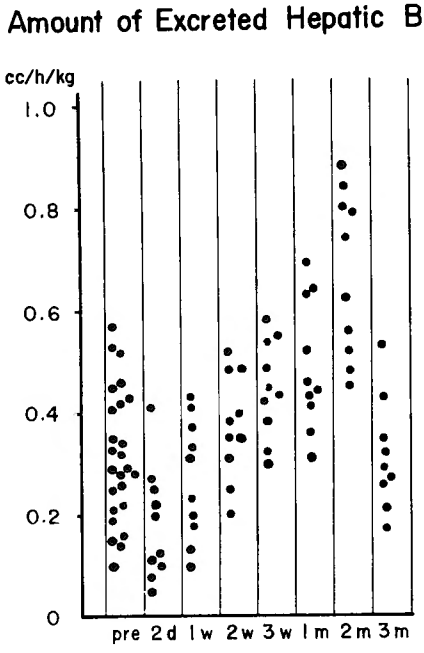


Fig. 7 Amount of hepatic bile excretion decreased after surgery, and increased remarkably 2 months after surgery, restoring to normal 3 months after surgery.

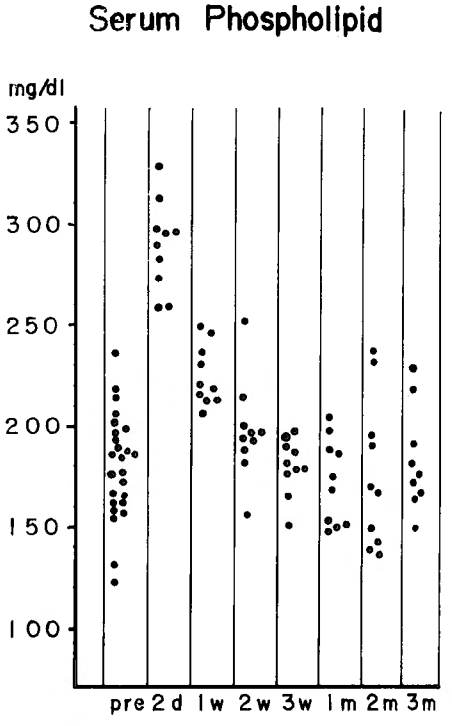


Fig. 8 Serum phospholipid level increased markedly immediately after surgery, and it returned to normal 3 weeks after surgery.

Tab. 8 Amount of Excreted Hepatic Bile (cc/h/kg)

Dog No. \ Time after Surgery	pre	2d	1w	2w	3w	1m	2m	3m
16	0.15	0.05	0.10	0.25	0.30	0.31	0.52	
2	0.53	0.41	0.43	0.52	0.58	0.69	0.80	0.53
19	0.19	0.11	0.23	0.35	0.48	0.43	0.79	0.43
28	0.14	0.08	0.13	0.31	0.42	0.46	0.56	0.17
5	0.45	0.27	0.41	0.48	0.54	0.63	0.84	0.29
18	0.21	0.12	0.20	0.20	0.32	0.41	0.48	0.26
9	0.22	0.10	0.18	0.38	0.45	0.61	0.74	0.35
31	0.29	0.20	0.31	0.35	0.38	0.36	0.45	0.21
34	0.46	0.22	0.33	0.48	0.55	0.52	0.88	0.32
23	0.35	0.25	0.37	0.40	0.43	0.44	0.62	0.27
Mean	0.32	0.18	0.27	0.37	0.45	0.49	0.67	0.31

Tab. 9 Serum Phospholipid (mg/dl)

Dog No. \ Time after Surgery	pre	2d	1w	2w	3w	1m	2m	3m
16	175	281	215	193	151	148	150	
2	167	258	231	157	165	150	139	174
19	161	272	220	201	194	154	195	181
28	185	312	248	215	190	188	190	150
5	196	296	235	195	181	186	169	191
18	155	288	212	182	177	175	143	165
9	198	295	218	192	188	197	237	218
31	159	259	211	197	178	151	137	176
34	161	327	245	251	197	205	233	229
23	165	295	205	187	178	168	169	168
Mean	180	288	221	197	180	172	176	181

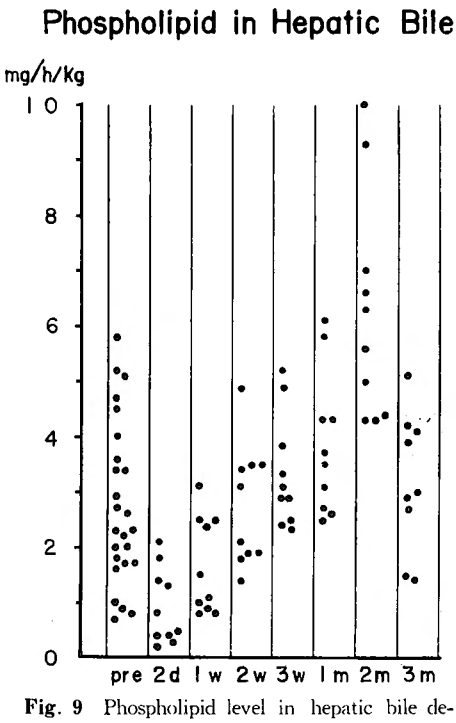


Fig. 9 Phospholipid level in hepatic bile decreased after surgery, and it increased remarkably 2 months after surgery, restoring to preoperative level 3 months after surgery.

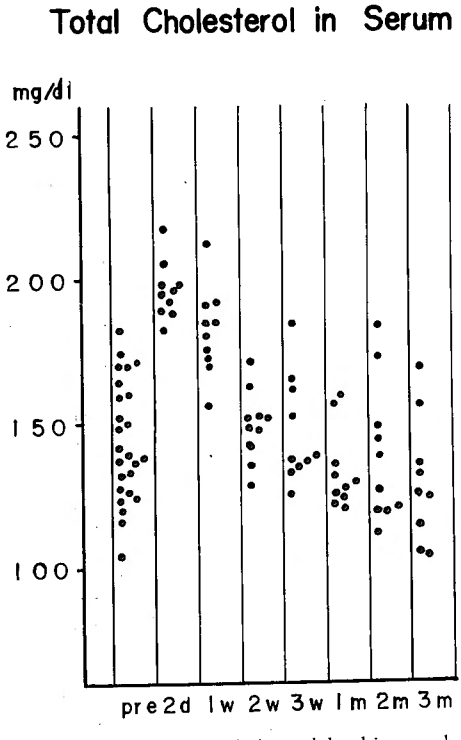


Fig. 10 Serum total cholesterol level increased remarkably immediately after surgery, and restored to normal 2 weeks after surgery.

Tab. 10 Phospholipid in Hepatic Bile (mg/h/kg)

Time after Surgery / Dog No.	pre	2d	1w	2w	3w	1m	2m	3m
16	0.7	0.4	1.0	1.4	2.4	2.5	5.0	
2	1.6	0.2	0.9	1.8	2.3	2.6	4.3	3.9
19	1.7	0.8	1.5	2.1	2.5	3.1	5.6	1.5
28	1.7	0.4	0.8	1.9	2.8	2.7	4.3	1.4
5	2.9	1.4	2.5	3.1	3.1	4.3	7.0	5.1
18	1.0	0.5	1.1	3.4	4.8	6.1	6.3	2.9
9	0.9	0.3	0.8	1.9	2.8	3.5	9.3	4.2
31	2.0	1.3	2.4	3.5	3.3	4.3	6.6	2.7
34	1.5	2.1	3.2	4.9	5.2	5.8	10.0	4.1
23	2.3	1.8	2.5	3.5	3.8	3.7	4.4	3.0
Mean	2.8	0.9	1.7	2.8	3.3	3.9	6.3	3.2

Tab. 11 Total Cholesterol in Serum (mg/dl)

Time after Surgery / Dog No.	pre.	2d	1w	2w	3w	1m	2m	3m
16	128	217	191	135	137	125	126	
2	137	194	185	148	135	135	119	125
19	141	182	173	151	132	124	148	135
28	132	198	212	142	184	127	144	124
5	143	192	185	171	165	156	138	132
18	123	189	170	128	125	121	119	124
9	159	205	192	152	161	159	183	156
31	148	196	175	151	137	120	111	114
34	126	188	156	162	152	131	172	168
23	150	198	180	147	138	129	120	135
Mean	145	196	182	149	147	133	138	135

after surgery, 133 mg/dl 1 month after surgery, 138 mg/dl 2 months after surgery and 135 mg/dl 3 months after surgery, restoring to normal about 2 weeks after surgery.

10. Cholesterol-Ester Ratio in Serum

As shown in Fig. 11, Tab. 1 and Tab. 12, preoperative maximum value was 79.5 per cent, the minimum value was 65.5 per cent and average value was 73.5 per cent. Two days after hepatic resection, the maximum value was 63.1 per cent, the minimum value was 50.2 per cent and average value was 57.9 per cent, the value markedly decreasing. The average value was thereafter 69.1 per cent 1 week after surgery, 75.5 per cent 2 weeks after surgery, 77.3 per cent 3 weeks after surgery, 81.3 per cent 1 month after surgery, 76.7 per cent 2 months after surgery and 74.8 per cent 3 months after surgery. Namely, the value returned to preoperative level 2 weeks after surgery, which further increased on to its peak 1 month after surgery and then decreased later than 2 months after surgery restoring to normal.

11. Total Cholesterol Level in Hepatic Bile

As shown in Fig. 12, Tab. 2 and Tab. 13, preoperative maximum value was 0.14 mg/h/kg body weight, the minimum value was 0.02 mg/h/kg body weight and average value was 0.07 mg/h/kg body weight. Two days after surgery, the maximum value was 0.10 mg/h/kg body weight, the minimum value was 0.03 mg/h/kg body weight and average value was 0.067 mg/h/kg body weight, showing slight decrease. The average value thereafter was 0.06 mg/h/kg body weight 1 week after surgery and 0.058 mg/h/ky body whight 2 weeks after surgery, decreasing on further. Three weeks after surgery, the average value was 0.09 mg/h/kg body weight and 1 month after surgery, it was 0.12 mg/h/kg body weight, slightly increasing. Two months after surgery, the maximum value was 0.22 mg/h/kg body weight, the minimum value was 0.10 mg/h/kg body weight and average value was 0.17 mg/h/kg, showing marked increase of 2.3 times of preoperative average value. Three months after surgery, the average value again decreased and restored to preoperative level, being 0.09 mg/h/kg body weight.

12. Total Bile Acid Level in Hepatic Bile

As represented in Fig. 13, Tab. 2 and Tab. 14, preoperative maximum value was 11.3 mg/h/kg body weight, the minimum value was 2.2 mg/h/kg body weight and average value was 5.8 mg/h/kg body weight. Two days after hepatic resection, the maximum

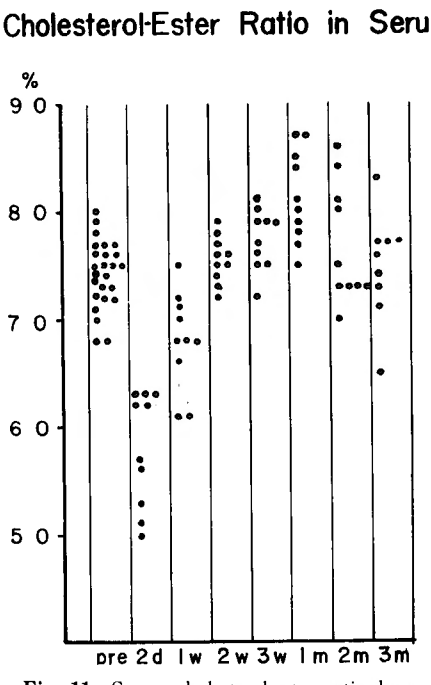


Fig. 11 Serum cholesterol-ester ratio decreased remarkably immediately after surgery, and restored approximately to preoperative level 2 weeks after surgery, reaching the maximum 1 month after surgery, which again decreased more than 2 months after surgery to restore to normal.

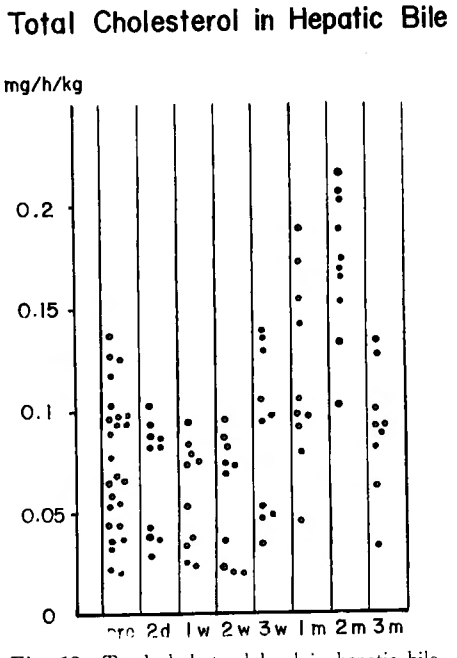


Fig. 12 Total cholesterol level in hepatic bile decreased after surgery, and increased markedly 2 months after surgery, returning to normal 3 months after surgery.

Tab. 12 Cholesterol-Ester Ratio in Serum (%).

Dog No. \ Time after Surgery	pre	2d	1w	2w	3w	1m	2m	3m
16	73.5	56.4	69.8	72.5	78.8	87.0	73.2	
2	75.1	61.5	68.2	73.8	79.1	87.4	69.7	73.8
19	72.2	51.3	72.1	71.5	76.9	83.8	72.9	73.2
28	71.3	62.8	61.3	78.9	80.2	78.5	85.7	82.7
5	70.8	50.2	71.4	78.1	72.3	76.9	79.7	70.6
18	78.1	62.6	75.1	76.3	75.4	78.4	84.0	75.6
9	77.1	63.1	68.4	77.4	80.9	85.1	80.9	76.9
31	75.2	56.8	60.9	75.3	76.2	79.5	71.7	77.2
34	72.2	62.0	75.6	76.2	71.5	80.7	73.3	77.4
23	77.3	52.5	68.3	75.1	78.9	75.2	72.5	65.9
Mean	73.5	57.9	69.1	75.5	77.3	81.3	76.7	74.8

Tab. 13 Total Cholesterol in Hepatic Bile ($\times 10^{-2}$ mg/h/kg)

Dog No. \ Time after Surgery	pre	2d	1w	2w	3w	1m	2m	3m
16	1.4	3.8	3.2	2.1	3.5	1.6	10.2	
2	9.6	9.2	7.3	8.7	9.3	9.9	18.8	9.1
19	8.9	8.1	7.8	9.5	13.8	18.9	13.2	10.0
28	4.4	3.7	2.5	2.1	1.8	9.1	16.9	3.3
5	12.6	10.3	9.3	6.8	13.5	17.3	15.2	13.3
18	9.7	8.7	5.3	7.4	12.8	15.3	17.4	9.1
9	3.3	2.9	2.4	2.0	1.9	9.8	20.6	12.6
31	5.3	4.1	3.7	3.5	5.2	7.9	16.4	8.1
34	9.1	8.1	7.5	8.2	10.5	11.1	20.2	6.1
23	9.8	8.5	8.3	7.2	9.7	10.5	21.6	8.8
Mean	7.1	6.7	5.7	5.8	8.8	11.7	17.1	8.9

Tab. 14 Total Bile Acid in Hepatic Bile (mg/h/kg)

Dog No. \ Time after Surgery	pre	2d	1w	2w	3w	1m	2m	3m
16	4.1	2.5	3.2	4.7	5.3	6.2	8.7	
2	7.5	3.1	6.8	7.7	8.5	9.3	10.5	5.8
19	2.5	1.5	2.8	3.5	3.8	4.8	6.5	4.1
28	2.3	1.2	1.9	2.8	4.7	5.9	6.2	3.6
5	8.5	4.7	7.2	8.5	8.2	9.1	15.4	7.8
18	3.5	2.1	3.1	5.2	6.3	8.0	10.1	5.2
9	2.5	1.4	2.7	3.5	7.3	10.1	16.9	12.3
31	5.8	3.5	1.8	6.3	8.9	14.5	17.5	11.0
34	9.1	5.3	7.1	9.7	11.6	11.5	13.0	6.1
23	4.7	3.1	4.3	6.2	6.0	8.7	11.8	5.5
Mean	5.8	2.9	4.4	5.8	7.1	8.8	11.7	6.8

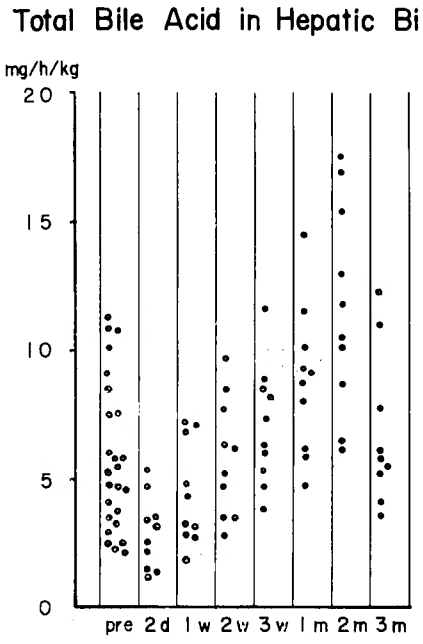


Fig. 13 Total bile acid content in hepatic bile decreased after surgery, and increased remarkably 2 months after surgery to restore to preoperative level 3 months after surgery.

value was 5.3 mg/h/kg body weight, the minimum value was 1.2 mg/h / kg and average value was 2.9 mg/h/kg body weight, showing remarkable decrease. The average value was thereafter 4.4 mg/h/kg body weight 1 week after surgery, 5.8 mg/h/kg body weight 2 weeks after surgery, 7.1 mg/h/kg body weight 3 weeks after surgery and then gradually increased, reaching 8.8 mg/h/kg body weight 1 month after surgery. Two months after surgery, the maximum value was 17.5 mg/h/kg body weight, the minimum value was 6.2 mg/h/kg body weight and average value was 11.7 mg/h/kg body whight, reaching 2.0 times of the preoperative average value. The value again decreased thereafter to 6.8 mg/h/kg body weight, on the average, 3 months after surgery.

13. Summary of the Results

Changes in the amount of hepatic bile excretion and constitution of bile in individual animals are summarized in Fig. 14, Fig. 15, Fig. 16, Fig. 17, Fig. 18, Fig. 19 and Fig. 20. Although there were some deviations among experimental animals, hepatic bile excreted from the residual liver parenchyma after hepatic resection showed a tendency in the early postoperative period to decrease both in its amount and in amount of each component of the blie, which, however, gradually increased to preoperative level and increased on thereafter surpassing the preoperative level in certain stadium, and finally restored to preoperative level again.

IV. DISCUSSION

By the functional examinations of the liver, which have hitherto been carried out, functional disturbance in the early period could be only demonstrated to some extent, concerning the fluctuation of liver function after hepatic resection. The results of these examinations still had some vague points and it has been difficult by these methods to disclose the fluctuation of the functional state after these data had returned to normal range. The present experiment was undertaken in the aim of deepening the understanding of the change in functional state in regenerative process of the residual liver parenchyma after hepatic resection, by pursuing the changes in amount of bile excreted from the residual liver parenchyma and in amount of each component of the bile together with common examinations as have been carried out.

There are two methods of bile collection, temporary collection and continuous collection. Temporary method has a disadvantage that its operative influence is larger, since the abdomen is opened to insert a tube into the biliary tract in order to make an observa-

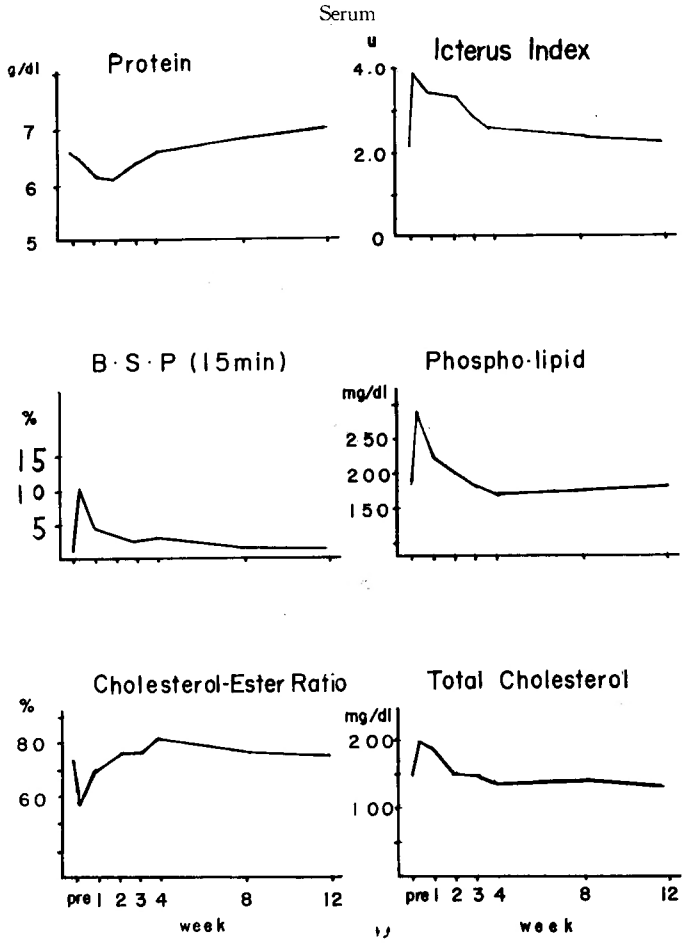


Fig. 14

tion on bile excretion. In continuous method of bile collection with external fistula, experiment can be carried out after influence of operation is made almost negligible. However, there appear various changes due to extracorporeal loss of the entire bile such as rapid decrease in amount of bile excretion[22)~24)], temporary decrease and later increase in bile acid elimination[25)~27)] and disturbance of digestion and absorption of fat. Both methods of bile collection have advantageous as well as disadvantageous points. In the present experiment, collection of bile was repeatedly carried out with the lapse of time by inserting a tube into the biliary tract transduodenally, the abdomen being opened. In this method, influence of laparotomy procedure cannot be neglected. However, efforts were paid to lessen the influence of laparotomy as much as possible, by closing duodenal incision and abdomianl wall, except small hole for inserted tube, during the collection of bile. By this method, collection of bile could have been repeated from 6 to 7 times in an individual animal with the lapse of time after hepatic resection. It is assumed that this method is suitable for long-term observation, without encountering various disturbances due to extracorporeal loss of bile through external biliary fistula, since the animals can be left in

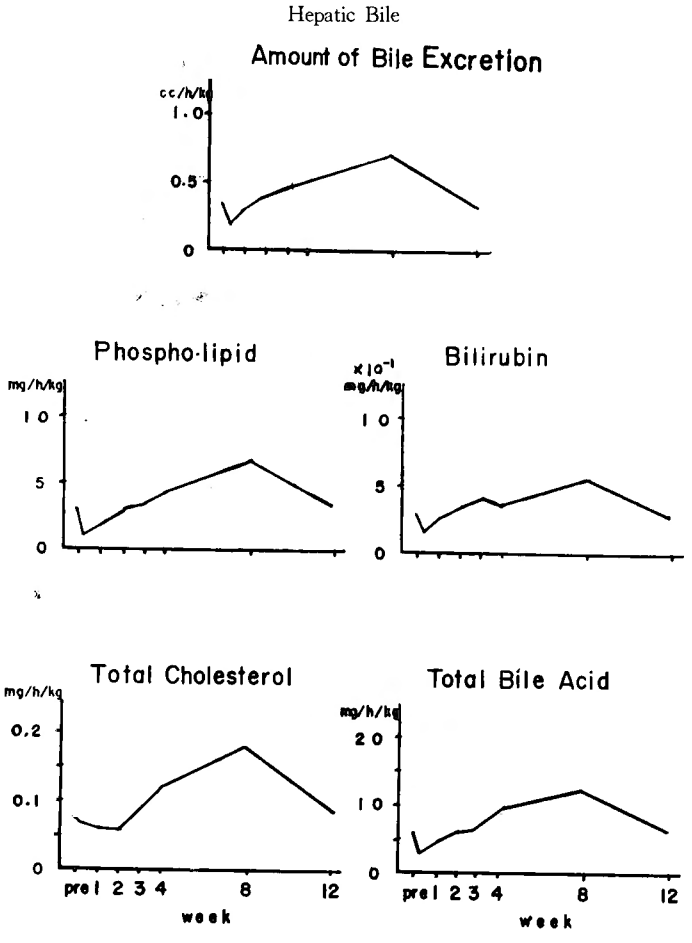


Fig. 15

nomal condition until the next bile collection.

It is assumed to be unjustifiable to grasp subtle changes from average values of each component of bile in a few normal animals, since there exists large individual difference in components of bile of dogs, and it was considered in the present experiment that obtained pre- and postoperative values should always be compared[28]. Since it was supposed that bile excretion might be altered in this method of collection when carried out without anesthesia[29][30], bile was collected in the present experiment under intravenous anesthesia with isozol which has been said to have little influence on the internal pressure of the biliary tract.

Although there is assertion that bile is excreted periodically[31]~[33], it is generally considered to be excreted continuously[24][29][34]~[36]. It is, however, known that bile excretion decreases in the fasting state, while asleep, in starvation and when hepatic temperature is low[37][38].

Concerning bile excretion during 24 hours in dogs, McMaster and others[24] reported to be from 3.5 to 9.5 g/kg body weight, Winogradow[39] to be from 10.6 to 16.1 g/kg

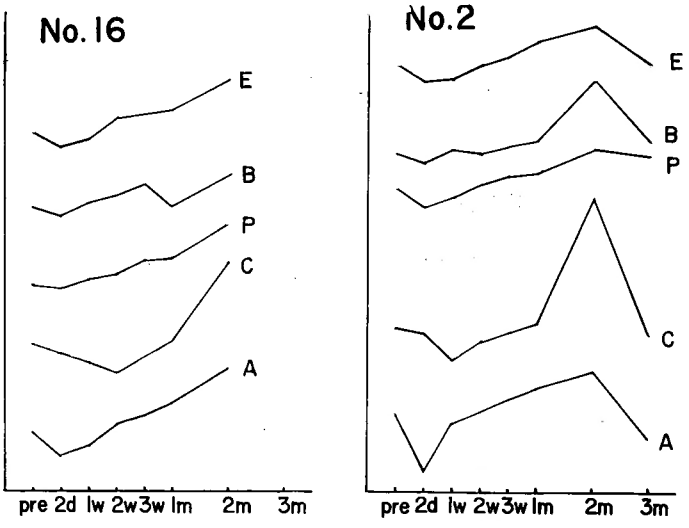


Fig. 16

E : Amount of Bile Excretion
B : Bilirubin
P : Phospholipid
C : Total Cholesterol
A : Total Bile Acid

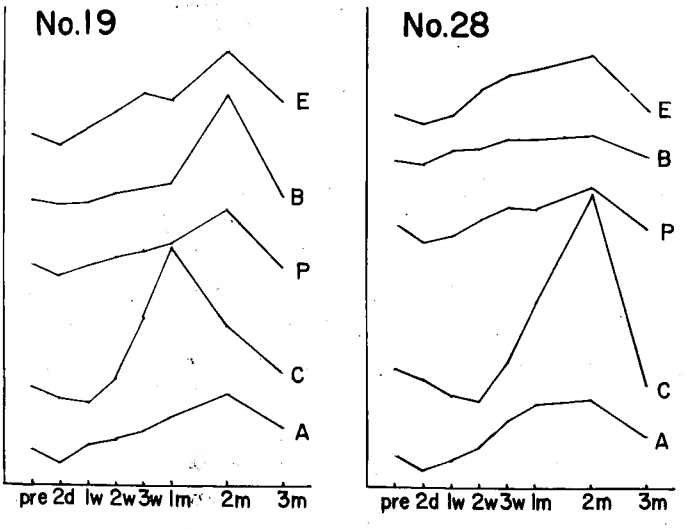
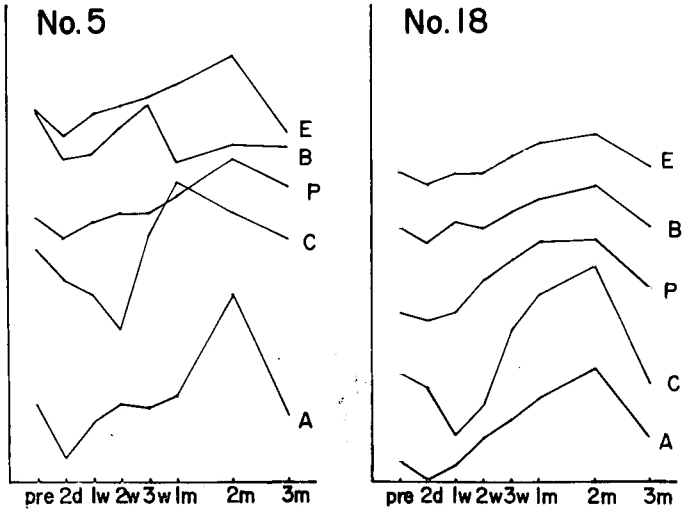


Fig. 17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E
B
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Fig. 18

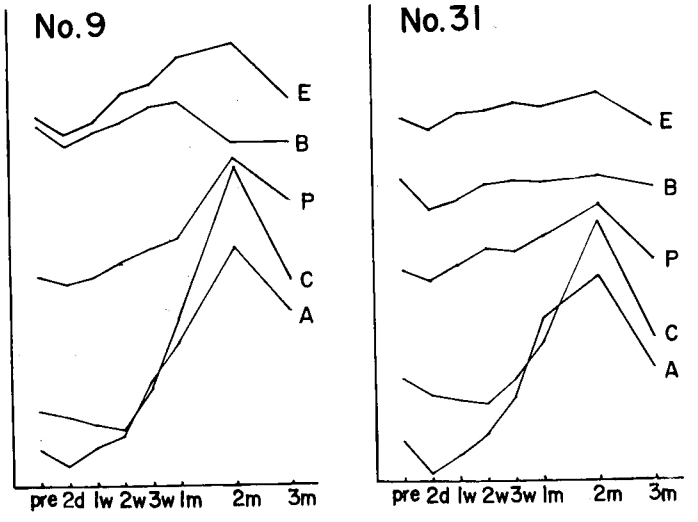
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Fig. 19

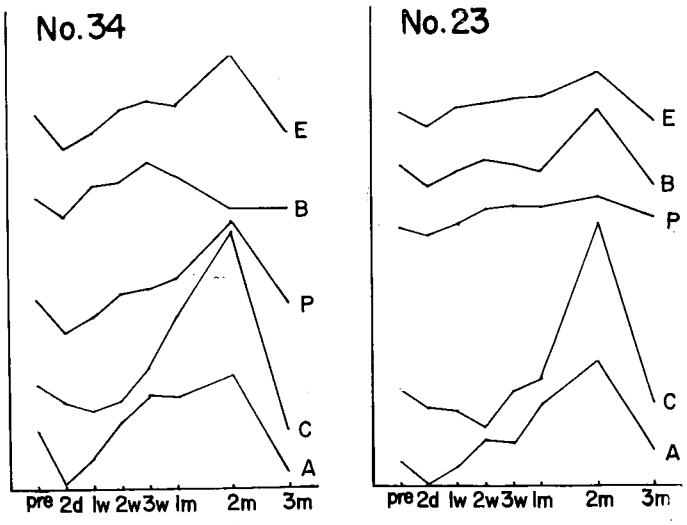

Fig. 20

body weight, BIDDER and SCHMIDT to be from 15.9 to 28.7 g/kg body weight and SAKURAI[40] to be from 3.4 to 25.0 g/kg body weight, indicating considerably large difference among these reports. COOK et al[41]. and HORIUCHI[42] also reported that bile is continuously excreted in certain rate, the former showing the data of 0.26 ± 0.024 cc/kg/h, the latter showinf the average date of 20 cases of 0.26 ± 0.12 cc/kg/h.

Presuming from the fact that excretion of bile is done under higher pressure than blood pressure, BRAUER[43] and WHEELER[44] reported that bile excretion from hepatic cells is not exerted by mere filtration of diffusion but by some active mechanism, and cellular regulation for the excretion is obviously based on utilization of energy.

In the present experiment, amount of hepatic bile excretion in the fasting state of dogs was 0.32 ± 0.12 cc/h/kg body weight, showing relatively constant value, on the average of 25 dogs. The amount of the excretion decreased to a half 2 days after hepatic resection, which was considered to be attributable to reduction of bile excreting liver prenchyma caused by hepatic resection and temporary disturbance of function of the residual liver parenchyma. Although a tendency of increase was observed in serum bilirubin at this stadium, it did not develop so far to manifest jaundice, and it was considered that elimination of bile was fairly compensated by the residual liver parenchyma corresponding to 50 per cent of the entire liver. In parallel with regeneration of the residual liver parenchyma, amount of bile excretion restored thereafter to preoperative level, which further increased on to reach approximately 2.2 times as much of preoperative level 2 months after hepatic resection. This phenomenon was interpreted that bile excretion increased as the result of prosperous energy metabolism going on in hepatic regenerative cells 2 months after hepatic resection. Later than this period, amount of bile excretion returned roughly to preoperative level 3 months after hepatic resection.

Since the theory of van den BERGH[45], it has been believed that the source of bilirubin mainly consists in hemoglobin derived from docomposition of red blood cells in the liver, spleen and bone marrow[46], and it is eliminated from liver cells to the intestine. MCNEE[47]

disapproved of the theory that bilirubin is produced in hepatic cells and he insisted that it is produced in the reticuloendothelial system chiefly existing in the liver, spleen and bone marrow. YAMAOKA[48)49)50)] successfully isolated an enzyme hemoglobin oxidase participating in decomposition of hemoglobin from the liver and he postulated that the process from hemoglobin to bilirubin principally proceeds in liver cells. As has been surveyed, the liver largely participates in production of bilirubin from hemoglobin. Although extrahepatic production of bile is ascertained, the amount is too small to take into consideration[51)]. Most part of bilirubin in bile is coupled with glucuronic acid and in microsome fraction of hepatic cells enzymes necessary for this coupling is contained[52)~56)]. For elimination of bilirubin, it is indispensable that bilirubin is coupled with glucuronic acid[57)], and up to present, no other bilirubin of direct type is demonstrated than glucuronic acid coupling in bile. However, there are some researchers as LONDON and others[58)59)] who suspect bilirubin production within liver cells themselves, and there remains much to be solved concerning production of bilirubin[60)]. Since there is large deviation in the amount of bilirubin in hepatic bile after resection of the liver, all the experimental animals did not show always exactly the uniform tendency. However, in most of the experimental animals, the amount of bilirubin eliminated in the early period after hepatic resection, at the time when hepatic function showed disturbances, decreased and it remarkably increased 2 months after surgery and finally restoring to normal 3 months after surgery. Namely, 2 months after hepatic resection, it was presumed that metabolic activity of liver cells was more prosperous than normal.

Phospholipid is mainly synthesized in the liver and intestine, and most part of phospholipid in plasma is from the liver[61)]. As demonstrated by KENNEDY and others[62)], lecithin is synthesized from fat of the liver. Although pathway of decomposition of phospholipid in organism, it is obviously accepted that the liver is the principal organ of synthesis and decomposition of phospholipid. Some part of phospholipid is eliminated in bile[63)], but in the past it has been supposed that biliary phospholipid content is small[64)~66)]. POPPER[67)] maintained that phospholipid content in hepatic bile does not exceed 0.1 mg/dl and it has little influence on serum phospholipid level. However, it was clarified by ISAKSSON and ZILVERSMIT[63)] that phospholipid in hepatic bile exists either in equal or larger proportion to that in plasma and it is directly excreted from the liver into bile without passing through blood stream[68)]. More than 95 per cent of phospholipid in bile is nothing but lecithin, and in bile of normal dogs its content as lecithin is 12 2 mg/cc[68)] and it was 8 9 mg/cc on the average of 25 dogs in the present experiments.

Phospholipid in bile plays an important role in absorption of fat[71)] and it forms micel by combining with bile acid[72)~74)]. Thus, it is the important component for dissolving cholesterol in bile. Serum phospholipid does not reveal noticable change even in parenchymal impairment of the liver, and does not reflect sharply hepatic disturbance. Phospholipid synthesizing ability of the liver is not affected seriously at hepatic disturbance. Fluctuation of serum phospholipid can be accepted as an indicator of phospholipid synthesis in the liver. However, it is not always rational to interpret in that way, since excretion of phospholipid from the liver is exerted in the 2 direction into blood stream and into bile.

BUSSY-CAPARI and others[75] observed a decrease in serum phospholipid in hepatic disturbance caused by carbon-tetrachloride, and they considered that its increase is associated with recovery of histological impairment of the liver. TAKAMI[76] asserted that low content of serum phospholipid is attributable to disturbance of phospholipid synthesis which is the domonstration of functional disturbance of the liver. In the present experiment, an increase in serum phospholipid was observed in the early period after hepatic resection, which is interpreted that among various disturbed liver function in the early period after hepatic resection, synthetic capacity of phospholipid alone might be contrariwise increased. However, phospholipid content in bile decreased in the early period after hepatic resection, and it increased exceeding the normal level 2 months after surgery when metabolic activity of regenrated liver cells was prosperous. At this stadium, no marked change could be observed in serum phospholipid content. Concerning the correlation between phospholipid content in bile and serum, little is known. However, fluctuations of these two after hepatic resection, as clarified in the present experiment, will provide some basic understandings for disclosing the relationship between there two.

Synthesis of cholesterol is mainly performed in the liver on the basis of acetic acid, more than 75 per cent of which turns into bile acid within the liver[77]. A part of cholesterol synthesized in the liver is eliminated into blood stream and another part into bile [78][79] A part of cholesterol entered the intestine is reabsorbed and join to enterohepatic cycle of cholesterol[80]. Thus, the liver is the central organ of cholesterol metabolism, and the relation between the liver and cholesterol is so intimate. SHINOI[81] also maintained that there exists close correlation between liver function and cholesterol content in bile, and biliary cholesterol decreases at functional disturbance of the liver. BYERS[82] and FRIEDMANN[83] reported that cholesterol synthesis of the liver is disturbed by hepatic resection and impairment caused by carbon-tetrachloride. At experimental impairment of the liver, when it is partial or slight, cholesterol synthesis increases and it is disturbed when the impairment is serious or in the occasion of ligation of the common bile duct. In parenchymal impairment of the liver, there appears hypercholesteremia and serum cholesterol-ester ratio decreases[84].

Owing to parenchymal disturbance of the liver and disturbance of hepatic cellular activity immediately after hepatic resection, cholesterol synthesis of the liver is disturbed with resulting decrease in cholesterol elimination in bile. It is because of disturbance of decomposition of cholesterol in the liver and elimination into bile that serum cholesterol shows an increase. At regeneration of liver parenchyma, synthesis of cholesterol is remarkably increased due to hyperfunction of liver cells, and it comes to be manifest as the increase in cholesterol in bile. The degree of this increase in cholesterol is in parallel with the functional state of the liver. In the present experiment, cholesterol in bile decreased in the stadium in which hepatic disturbance was utmost remarkable after hepatic resection, and it restored concurrently with liver regeneration, showing marked increase exceeding preoperative level in a certain period. This finding is interpreted to indicate that there exists a stadium in the process of liver regeneration in which metabolic activity of liver cells conspicuously increases.

It has been demonstrated by many experimental studies of BLOCH, BERG, RITTENBERG[85]

and others that bile acid is produced from cholesterol in liver cells[86]. About 90 per cent of bile acid excreted from the liver to the intestine is reabsorbed with the absorption of fat, thus forming entero-hepatic cycle of bile acid[87]. Most part of bile acid eliminated into bile is absorbed from the intestinal wall as lipoid, and then enters the portal blood flow, being isolated from lipoid. About 80 per cent of bile acid is eliminated into bile in a form of glycin or taurin coupling[88][89], and the coupling is performed in microsome fraction of liver cells, in which some energy is required[90][91]. Production of bile acid in the liver is regulated to be constant by the amount of bile acid which is once reabsorbed and returns to the liver via the portal flow[92].

According to KAZUNO[93], amount of bile acid, which participates in entero-hepatic cycle, is small, corresponding to less than half of bile acid which reaches the intestinal canal, and most part of bile acid is destructed within the body. The principal sites of destruction of bile acid in the body are the liver and intestine[86][94]~[96], and accordingly, the amount of bile acid produced everyday in the liver is extraordinarily large. When liver cells encounter some impairment, amount of bile acid in bile decreases markedly, which is due to decrease in bile acid production caused by cellular impairment of the liver[86]. In the metabolism of bile acid also, the liver occupies a large role. In the present experiment, bile acid production was reduced in the stadium of serious impairment of liver cells after hepatic resection, with resulting decrease in bile acid in bile. In parallel with the recovery of liver function at liver regeneration, bile acid elimination remarkably increased in bile, which was presumed to be due to increase in metabolic activity of the regenerated liver cells with resulting increase in bile acid synthesis in liver cells. It is further presumed that there exists a certain stadium of temporary hyperfunction in the process of liver regeneration.

Amount of bile excretion, that of bilirubin in bile, that of phospholipid in bile, that of cholesterol in bile and that of total bile acid, all these are largely influenced by the condition of liver function, and the liver being central organ of metabolism of these components, when the metabolic activity is decreased, synthetic capacity of liver cells also is reduced with resulting decrease in these components in bile, whereas in the stadium of prosperous activity of liver cell, synthetic capacity of liver cells is also accentuated with resulting increase in these components in bile. It is assumed that this stadium of increase in these components in bile coincides with the stadium of temporary excessive hypertrophy of the regenerated liver parenchyma after hepatic resection. It is considered interesting that once increased these components of bile restore to preoperative level 3 months after hepatic resection, presumably owing to regulatory mechanism of hepatic regeneration and metabolisms of the liver, and this might be a problem to be clarified for accurate understanding of pathophysiology of liver regeneration.

V. SUMMARY

After 50 per cent of the liver was resected in dogs, analysis was made on hepatic bile and blood with the lapse of time until 3 months after the resection, and some new findings were obtained, which were not clarified by functional examinations of the liver as have hitherto been carried out.

I. Changes in the amount of hepatic bile excretion and various components in bile

1. Amount of hepatic bile excretion

Amount of hepatic bile excretion decreased immediately after the hepatic resection, which increased thereafter gradually reaching 2.2 times of preoperative level 2 months after the resection. It decreased again, restoring to preoperative level 3 months after the resection.

2. Amount of bilirubin in bile

Amount of bilirubin in bile decreased immediately after the resection, and then increased gradually reaching 1.6 times of preoperative level 2 months after the resection, which restored approximately to preoperative level 3 months after surgery, although there was large individual fluctuation in this change in bilirubin amount in bile.

3. Amount of phospholipid in bile

Amount of phospholipid in hepatic bile decreased immediately after surgery, and it increased thereafter reaching 2.2 times of preoperative level, on the average, 2 months after the resection, which again decreased thereafter restoring to preoperative level 3 months after the resection.

4. Amount of total cholesterol in bile

Amount of total cholesterol in hepatic bile gradually decreased after the resection reaching the lowest level 2 weeks after the resection, and it increased to 2.4 times of preoperative level, on the average, 2 months after the resection, which decreased thereafter again restoring to preoperative level 3 months after the resection.

5. Amount of total bile acid in bile

Amount of total bile acid in hepatic bile decreased immediately after the resection, and it increased gradually reaching 2.2 times, on the average, of preoperative level 2 weeks after the resection, which decreased thereafter again restoring to preoperative level 3 months after surgerey.

II. Changes in serum examinations

As the indicator of liver function, serum protein level, B. S. P. retention test and serum cholesterol-ester ratio were examined, and all these examinations revealed abnormal findings in the early stadium after the resection, which, however, restored to normal from 3 to 4 weeks after surgery.

Icterus index, amount of phospholipid and total cholesterol content also revealed abnormal findings in the early stadium after surgery, there also restoring to normal from 3 to 4 weeks after surgery.

From the findings known from liver function tests such as B. S. P. rerention test, serum cholesterol-ester ratio, as have been carried out, it has been accepted that disturbed liver function caused by 50 per cent resection of the liver is improved in parallel with regeneration of the residual liver parenchyma and restores to preoperative normal function from 3 to 4 weeks after surgery. In the present experiment, however, based on the observation on the fluctuation of amount of hepatic bile excretion, bilirubin level in bile, total cholesterol level in bile and total bile acid level in bile, all of these decreased in the early stadium after the resection and had correlation with the findings of liver function tests, and they increased thereafter remarkably surpassing preoperative level 2 months after

surgery, which decreased restoring to preoperative level 3 months after surgery. From these findings, it was assumed that there exists a certain period of temporary hyperfunction in the process of liver regeneration after hepatic resection.

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(* in Japanese)

和文抄録

再生肝の胆汁分泌能についての実験的研究

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肝切除の実験的研究は1882年 Gluck が肝1/3切除は安全に行ないうると発表して以来，肝切除の病態生理に関して，多くの研究がなされているが，肝再生の過程において機能的にいかなる変遷を示すかという点については従来の諸肝機能検査では，早期の機能低下をある程度示すのみで，検査成績で正常いきに回復したことをばく然と知り得るのみであつた．

著者は肝切除後，経過を追つて肝から排せつされる肝胆汁を検索することによつて，再生肝の機能状態の変遷を更に解明しうるものと考え，本実験に着手した．

犬の肝の1/2切除を行ない，術前から術後3ヵ月まで経時的に採取した肝胆汁と血液を分析して次の結果を得た．

1) 胆汁分泌量は術直後に減少するが，以後次第に増加して2ヵ月後には術前の約2.2倍に増量し，以後再び減少して3ヵ月後にほぼ術前値に復した．

2) 胆汁 Bilirubin 量は術直後に減少するが，以後次第に増加して2ヵ月後には術前の約1.6倍に増量し，以後再び減少して3ヵ月後にはほぼ術前値に復した．

3) 胆汁りん脂質量は術直後に減少し，以後次第に増加して2ヵ月後には平均して術前の約2.2倍に増量し，以後再び減少して3ヵ月後にはほぼ術前値に復した．

4) 胆汁総 Cholesterol 量は術直後より次第に減少して2週間後に最も減少し，以後次第に増加して2ヵ月後では平均して術前の約2.4倍に増量し，以後再び減少し，3ヵ月にはほぼ術前値に復した．

5) 胆汁総胆汁酸量は術直後に減少し，以後次第に増加して2ヵ月後には平均して術前約2.2倍に増量し，以後再び減少して3ヵ月後にはほぼ術前値に復した．

6) 肝機能検査として行なつた血清たん白質，B. S. P. 試験，血清 Cholesterol-Ester 比は術後早期には異常所見を示すが，3～4週後には正常に復した．黄だん指数，りん脂質量および総Cholesterol 量も術後早期には異常所見を示すが，3～4週後にはいずれも正常値に復した．従来からの肝機能検査として実施されている B. S. P. 試験，血清 Cholesterol-Ester 等の変動からは50%肝切除により低下した肝機能が，残存肝の再生と共に改善されて，約3～4週間で術前の正常機能に復するものと考えられていたが，本実験で検索した肝胆汁の分泌量，Bilirubin 量，りん脂質量，総 Cholesterol 量および総胆汁酸量の消長を検索した結果，肝切除後早期にはこれらは減少して，肝機能検査成績と相関々係を示したが，以後次第に増量して2ヵ月後にはいずれも術前値をはるかにしのぎ，これらが術後3ヵ月で術前の level に復するという現象が観察された．この事実から肝切除後の残存肝は再生の過程において，機能こう進の状態を示す時期があるものと考えられる．