The relatively small range of variations in the absolute amount of bilirubin secreted with the bile may be explained as being due to its being a degradation product of hemoglobin, a relatively constant level of which is essential for the proper functioning of the organism. It is known that a certain parallellism exists between the amount of hemoglobin in the blood and the amount of bilirubin secreted with the bile [6]. This relative constancy is apparently a consequence of the role of bilirubin in hemopoiesis, since it has been found that one of the conditions for the proper functioning of the hemopoietic process is the normal secretion of bilirubin into the intestine [7]. It is evident that the process of formation of the bile pigments depends on complex biochemical processes, which proceed continually, chiefly in the liver. It may be thought that the changes in the functional state of the cerebral cortex produced in our experiments were of insufficient magnitude to influence the formation of bile pigments. Were such relatively slight changes in cortical function as are associated with the elaboration of a conditioned reflex, or with its differentiation, to be able significantly to affect the course of complex metabolic processes in the organism, we would expect there to be continual and violent fluctuations in the composition of the internal medium of the organism. We know, however, that organisms maintain the constancy of their internal medium with great precision.

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BILE SECRETION AFTER PARTIAL RESECTION OF THE LIVER OF DOGS WITH AN EXTERIORIZED COMMON BILE DUCT

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Structural changes taking place in the liver during the process of its regeneration following traumatic injury have been studied in a number of mammalian species [3, 5, 6, 8, 9, 10]. During reparative regeneration of the mammalian liver the resected portion of the organ is not restored, although the final weight and size of the liver are the same as initially, as a result of intensive proliferation of the surviving tissue. This mode of regeneration has been termed regenerative hypertrophy by M. A. Vorontsova [1].

While the histogenesis of hepatic regeneration has been the subject of numerous researches, only a very few papers have been devoted to the study of alterations in the functional activity of the liver after its traumatization and during the subsequent regenerative process [7]. This problem is, however, of considerable current interest, in particular for surgical practice [2, 4]. A study of the functional changes parallel with the morphological ones encountered during regeneration of the liver would permit of a correlated morphophysiological treatment of the process.

We investigated the alterations in the bile secreting function of the liver during regeneration following traumatic injury. The experiments were performed on 1-2 year-old dogs.

* In Russian.

EXPERIMENTAL METHODS AND RESULTS

After exteriorizing the common bile duct, by I. P. Pavlov's method, we determined the normal secretion of bile in response to meat, recording the amount secreted in 15 minute intervals, its color, opacity, and bilirubin and cholesterol content. Partial resection of the liver was then performed, after which bile secretion again followed.

After exteriorization of the common bile duct the dog Dik produced from 4.5 to 18.7 cc of bile per hour, mean secretion 10 ± 0.83 cc. Part of the right anterior lobe of the liver was then removed. Secretion of bile began on the third day after the operation, as soon as the dog was put into the stand.

The first portion of bile was of a milky-yellow color, and the succeeding ones were of the ordinary color. The rate of secretion curve was level, without any abrupt fluctuations such as are typical of the normal curve. On the 6th day there was no latent period of bile secretion, and the bile was of the ordinary color; the 1 hour secretion was 19.5 cc. During the succeeding days, the amount of bile secreted diminished, gradually approaching the normal value.

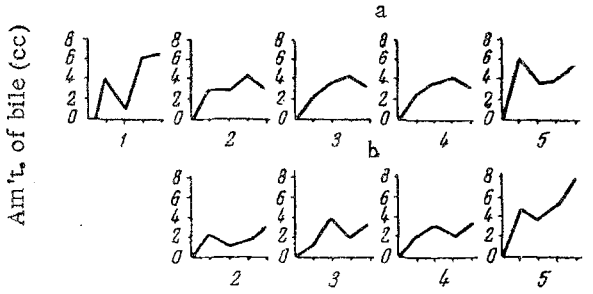

Fig. 1. Bile secretion in response to meat, after partial hepatic resection in the dog Borok. a) After resection of part of the right anterior lobe of the liver; b) after repeated resection of the right anterior lobe. 1) Before operation; 2) one day after operation; 3) 2 days after operation; 4) 3 days after; 5) 4 days after operation. Abscissa: time, in 15 minute intervals.

After exteriorization of the common bile duct the dog Borok produced 8.8 to 26 cc of bile per hour, a mean value of 16.2 ± 1 cc; the bilirubin content varied from 20 to 200 mg%, mean value 65 ± 20 mg%, and the cholesterol content was 80-230 mg %.

Part of the right anterior lobe of the liver was removed from this dog. During the first few days after the operation no latent period for secretion of bile could be observed. Approximately equal amounts were secreted at 15 minute intervals, so that the rate of secretion curve was horizontal (Figure 1, a). Five days after the operation the amount of bile secreted during 1 hour was 21.5 cc. The amount secreted had gradually returned to the normal value by the end of the second week. The bilirubin content was somewhat elevated after the operation (220 mg%). The cholesterol content was within normal limits.

The remainder of the right anterior lobe of the liver was removed from the dog Borok on the 44th day after the first operation.

A second operation, involving removal of the remainder of the right anterior lobe and of a portion of the left posterior lobe weighing 80 g, was performed on the dog Dik, 4 months after the first operation. The effects on bile secretion were similar to those seen after the first operation.

There were differences in the rate of secretion curves, for 15 minute intervals, which were not so level as after the first operation, and showed fluctuations which were not, however, as marked as for normal bile secretion (Figure 1, b). Apart from this, the normal pattern of bile secretion was reestablished much sooner than after the first operation (towards the end of the first week).

Similar changes were seen in the bilirubin and cholesterol contents of the bile.

After exteriorization of the common bile duct, the dog Belka secreted from 2.2 to 9.5 cc of bile per hour, mean secretion 6.3 ± 1.2 cc.

A portion of the left hepatic lobe weighing 32 g was resected (Figure 2, a). On the following day, in response to 200 g of meat, the bile secreted differed in successive portions: the 1st portion (0.8 cc) was watery and faintly colored, the 2nd (2.6 cc) was turbid and of a dark green color, and the 3rd (4.7 cc) separated into an upper, yellow layer and a lower, dark green layer, the 4th (0.4 cc) was turbid and greenish-white, and the 5th (0.5 cc) was stratified.

After another day, a great amount of watery, whitish fluid (white bile) began to flow from the duct, as soon as the dog was placed in the stand; 70 cc were secreted in 15 minutes, and 181 cc after an hour.

The fluid contained considerable amounts of greyish-white, flocculent precipitate. Microscopic examination of the deposit showed the presence of cell detritus, well-preserved sheets of common bile duct epithelium, and cholesterol crystals. The amount of deposit was greatest during the 2nd hour from the beginning of feeding.

After 2 days, feeding was immediately followed by secretion of white bile, in smaller amount than on the previous day, although still 10 times greater than the normal value; 81 cc of white bile were secreted over an hour. On this day three strata were visible in the bile: an upper, pale yellow layer, a middle, almost colorless one, and a lower, greyish-white one. Traces of bilirubin and cholesterol were found in the white bile.

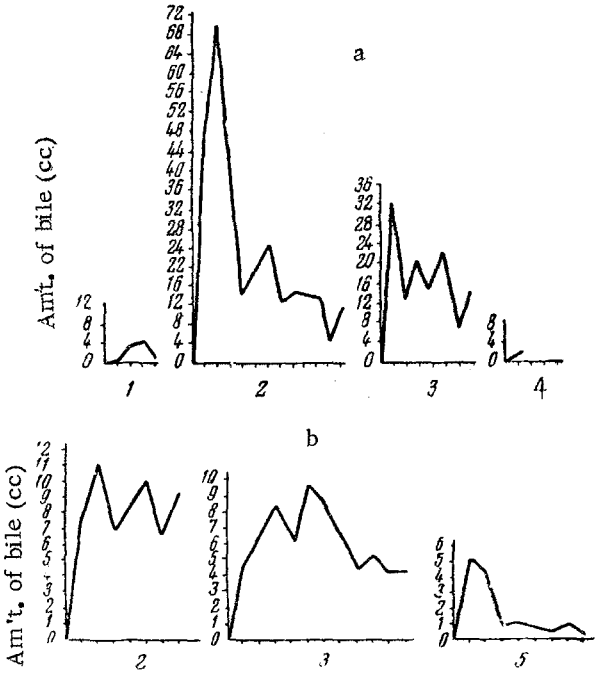

Fig. 2. Secretion of bile in response to meat after partial resection of the left hepatic lobe. a) Belka; b) Belyi. 1) On the day of operation; 2) 1 day after; 3) 2 days after; 4) 3 days after; 5) 4 days after the operation. Time scale as for Figure 1.

Nitrogen was determined in two portions of bile (with the least and the greatest amount of deposit), by the Kjeldahl method. We found 0.0196 mg/ml of nitrogen in the portion containing less sediment, and 0.02 mg/ml in that containing more sediment.

After 4 days the dog was feeble, and lay down most of the time, being reluctant to stand up. It refused meat when placed in the stand, but drank some glucose water. Bile at once started to flow, being transparent, and of

a brownish-green color; 2.5 cc were secreted during 15 minutes. At the 18th minute the dog collapsed in the harness, and the experiment was abandoned. It died in acute dehydration, despite all measures taken to save it.

At autopsy we found acute dehydration of the tissues, with atrophy of the muscles. The bile ducts were patent, and viscous, dark green bile could be expressed from the gall-bladder. Microscopic examination of stained sections of the liver showed marked dilatation of the pericapillary spaces and of the capillaries, a disordering of the hepatic trabeculae, and degenerative changes in the liver cells.

After exteriorization of the common bile duct, the dog Belyi secreted from 5.9 to 8.6 cc of bile per hour, mean secretion 7.0 ± 0.5 cc, containing bilirubin 48-249 mg %, mean value 100±61 mg %, and cholesterol 80-869 mg %, mean value 137±47 mg %.

One after resection of a portion of the left anterior lobe of the liver, weighing 24 g, the dog began to discharge white bile, in the form of a turbid greyish-white fluid with a large amount of sediment. The volume of white bile was 4 times greater than the amount of bile usually secreted by this animal (Figure 2, b). Smears of the bile showed various cells, in a more or less advanced stage of degeneration, isolated cholesterol crystals, and microorganisms. The first portions of white bile contained less sediment, and the nitrogen content amounted to 6.95 mg/ml, corresponding to 43.48 mg/ml of protein; the nitrogen content of portions of bile giving a more copious sediment was 8.54 mg/ml, corresponding to 53.4 mg/ml of protein.

Two days after the operation, as soon as the dog was placed in the stand and given food, it began to discharge white bile, in slightly lesser amount than on the previous day, although still considerably more than before the operation. The bile collected on this day separated into 3 layers, as for the dog Belka.

After 4 days, ordinary bile was being discharged, being dark brown in the first portion, and light brown in the succeeding ones. On the following days the amount of bile secreted fell steadily, falling to zero on the 10th day. Flow of bile was renewed after 5 days, and became similar to that before the operation.

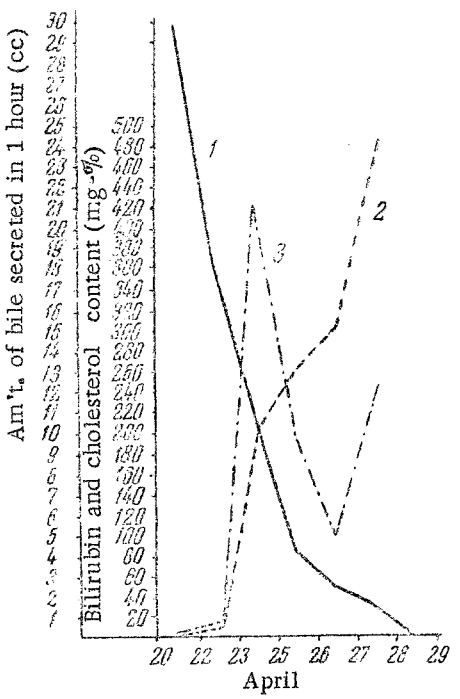

Fig. 3. Relation of the amount of bile secreted over 1 hour to its bilirubin and cholesterol contents, after partial resection of the left hepatic lobe of the dog Belyi, on April 20. 1) Amount of bile; 2) bilirubin content; 3) cholesterol content.

During the first 2 days the bilirubin content of the bile was very small (traces only). Thereafter, parallel with diminution in the volume of bile discharged, its bilirubin content rose to values considerably exceeding the normal ones (Figure 3). The cholesterol content was very small (traces) during the first two days, and was in the normal range thereafter (Figure 3).

DISCUSSION OF RESULTS

The disturbances in secretion of bile following partial resection of the liver may be considered in two groups: minor changes seen after removal of part of the right lobe, and after repetition of this operation, and major changes, manifested by discharge of white bile, following partial resection of the left hepatic lobe.

Our findings are evidence of the extraordinarily large compensatory capabilities of the liver, which is able, within a very short time after infliction of very considerable trauma, to restore its impaired functions, in particular that of bile secretion.

Different results were obtained for injury of the right and the left lobe, and this is probably due to their differences in blood supply. It may hence be concluded that, in operations involving surgery of the liver, not only the amount of tissue removed, but also its location, should be taken into consideration.

Disturbances of bile production are much less severe after repetition of the resection, and restitution of normal biliary function takes place much sooner.

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EFFECT OF THE DRUG TETAMON-I ON THE BILE SECRETING FUNCTION OF THE LIVER

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We showed in our previous communication [10] that Difenin, which hinders transmission of nerve impulses in N-cholinergic systems, exerts a marked inhibitory effect on the biliary function of the liver.

The present paper deals with the nature of the effect of Tetamon-I (tetraethylammonium iodide) on bile formation in the liver.

As has been shown by the work of K. M. Bykov, A. V. Rikkl , E. P. Ivanov, and S. L. Balakin [4, 5, 7, 9] and others, bile secretion is under the control of the central nervous system, and disturbances of the nervous connections between the central nervous system and the liver should lead to alterations in hepatic function.

Tetraethylammonium derivatives inhibit transmission of impulses in N-cholinergic systems of peripheral ganglions, chiefly of the parasympathetic system [1, 2, 3, 6, 8, 11].

EXPERIMENTAL METHODS

The experiments were performed on 4 dogs provided with permanent gall-bladder fistulae, and with ligated common bile ducts. Each experiment lasted 4 hours, and we determined the amount of bile secreted, and its bile acid content, for each hour. In the first series of experiments we examined the effect of Tetamon-I on spontaneous bile secretion, and in the second series we examined the effect during digestion. The injections of the drug were followed immediately by breakfast, consisting of 250 ml of milk and one large hen's egg. Tetamon-I was injected intravenously (in some experiments intramuscularly), in doses of 0.5-2 ml, corresponding to

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* In Russian.