CCCXI. THE RESORPTION OF THE BILE ACIDS FROM THE INTESTINES.

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THE circulation of the bile acids has been recognized for some time. Schiff [1870] showed that bile given *per os* acted as a cholagogue. Tschernoff [1884] pointed out that the cholic acids were partly resorbed from the intestines, carried to the liver and again secreted with the bile. Later this inference was made and experimentally supported by several investigators. Copeman & Winston [1889] and Pfaff and Balch [1897] showed that this circulation probably occurs even in man. From experiments with bile-fistula dogs Whipple & Smith [1928] concluded that of the bile acids normally excreted only about one-seventh was freshly formed, the rest having been resorbed and then carried to the liver.

Very little is known, however, about the mechanism of this resorption. Verzar & Kuthy [1930] have shown that the bile acids from the intestinal contents are partly adsorbed to the surface of the mucosa, whence they pass the outer cellular walls together with the fatty acids as water-soluble or molecular-disperse choleic acids. These compounds, however, must be at least partly decomposed already in the epithelial cells, because here fat globules in great quantities are microscopically visible after a fat meal. The liberated bile acids then, according to Verzar [1931], return to the lumen surface of the cells to combine with new fatty acids. Thus this theory accounts only for the first step in the resorption of the bile acids themselves.

The purpose of our experiments was to try to trace the further paths followed by the resorbed bile acids from the intestinal mucosa to the liver; either they might follow the fats in the lymph through the thoracic duct in the form of free bile salts or as choleic acids, or they might diffuse through the walls of the blood capillaries into the portal system. In the former case they would have to be mixed with the systemic blood before reaching the liver; in the latter case they would be carried by the portal blood directly to the liver. The scanty data in the literature bearing on this question give very conflicting information.

EXPERIMENTAL.

In our experiments we have, after laparotomy, injected strong bile acid solutions into the small intestines of animals. By following the bile acid contents of portal blood as well as of systemic (heart) blood we believe that we have been able to trace the paths of these acids.

The animals were anaesthetized during the whole experiment. The samples of systemic blood were always taken by heart puncture (with the exception of the horse, Table III). The portal samples were taken after laparotomy with a syringe with a very fine curved needle, and the hole was instantaneously closed with a small clamp. Before the injection we always took initial samples both of systemic and portal blood. The bile salts used were prepared according to O. Hammarsten and were very pure; some sodium phosphate was always added

Table I.

		Cholic acids in blood												
		Initial value	After injection											
			1 hour		2 hours		3 hours		4 hours					
Date	Animal	Wt. kg.	h.	p.	h.	p.	h.	p.	h.	p.	h.	p.		
			Injected into the intestines											
8. x.	Rabbit 2	1.8	1.0	—	2.2	6.3	2.4	3.6	—	—	—	—		
13. v.	Rabbit 3	2.9	1.0	3.0	4.4	14.2	3.8	14.2	—	—	—	—		
4. vi.	Rabbit 15	3.6	1.1	3.9	1.9	6.6	2.1	6.6	—	—	—	—		
4. vi	Cat 4	3.3	2.1	5.3	7.9	13.3	3.3	8.5	2.8	7.7	—	—		
15. vi.	Rabbit 28	2.7	1.3	2.8	1.4	8.6	1.7	5.1	—	—	—	—		
			10 ml. Na glycocholate 10 % + Na stearate 5 % + glycerol 5 %											
17. vi.	Cat 9	3.7	1.2	3.1	1.7	5.0	1.5	5.5	2.0	3.0	1.9	5.1		
			10 ml. Na glycocholate 10 % + Na oleate 5 % + glycerol 5 %											
19. vi.	Cat 10	3.2	1.1	2.1	1.1	4.3	1.4	6.0	2.5	5.0	1.1	4.8		
			10 ml. Na glycocholate 10 % + Na stearate 5 % + glycerol 5 %											

Table II.

Anaesthetics in both cases: avertin + ether.			Cholic acids in blood											
			After injection											
			Initial value		1 hour		2 hours		3 hours		5 hours			
			h.	p.	h.	p.	h.	p.	h.	p.	h.	p.		
Animal	Date of ligation	Wt. kg.	Injected into the intestines											
Cat 6	19. vi.	3.3	(1) 10 ml. water											
			(2) 10 ml. Na cholate 5%											
Cat 7	26. vi.	3.5	10 ml. Na cholate 5%											
	9. vii.		16.5	15.7	23.7	31.0	25.2	39.0	22.0	24.4	13.9	17.6		

Anaesthetics in both cases: avertin + ether.

to the solutions. The solution was injected through a fine needle into the jejunum. Between the portal blood-samplings the laparotomy was closed with clips so that the intestines should not become cold or dry. All the experiments were made between 12 noon and 6 p.m. The bile acid analyses were carried out according to Josephson [1935].

All the figures for the bile acid content of the blood are expressed as mg. per 100 ml. In the tables h. signifies systemic (heart) blood and p. means blood from the portal vein.

In Table I are given the results of some of the experiments on healthy animals.

The cholic acid values in the portal blood were always significantly increased after the injection of the bile salt solution into the intestine. In most cases the values in the systemic blood were also slightly increased. It must be mentioned that Greene *et al.* [1928] also found an increase of the bile acids in the portal blood after administration *per os*; their methods however were not very reliable.

In the hope of obtaining more decisive figures we have also tried to inject bile salt solutions into the intestines of animals with jaundice, caused by ligation of the common bile duct some time before the experiment. This plan was unsuccessful with rabbits, since they usually became very weak when jaundiced and always died during the second operation. With cats we had more success, and in Table II are given the results with two of these animals; cat 6 first received an injection of water as a control.

The increase of the bile acid content of the blood is of course much larger in these experiments in which their elimination was delayed, but the difference between portal and heart bloods is of the same order of magnitude as in the previous table.

As a complement to the blood values after resorption, we also wanted to analyse the chyle after injection of cholic acid into the intestines. For this purpose we could not use small animals, since 5 ml. of lymph were necessary for an analysis. We therefore examined samples of thoracic lymph from five different recently slaughtered cows. To our surprise we found that all the samples were devoid of detectable quantities of cholic acids, all the values being within the limits of error of the method, that is between 0 and about 0.3 mg./100 ml., yet cows normally have a rather high bile acid content in the blood, usually 3-4 mg./100 ml. It may be mentioned that with the method employed even those cholic acids are determined which are conjugated as choleic acids.

For the purpose of getting a lymph analysis after injection of bile salts into the intestines we now used a horse as test animal. The horse has a very large cisterna chyli, and the thoracic duct has a diameter of about 5 mm. We thus succeeded in getting 35 ml. lymph, 80 min. after the bile acids had been injected and shortly after the killing of the animal.¹ As anaesthetics chloral and

Table III.

17.i. Horse, about 500 kg. chloral + chloroform.

Injected into the intestine	Blood				Lymph	
	Initial value		1 hour		Chol. acids mg./100 ml.	Lipoids %
	h.	p.	h.	p.		
2 l. Na glycocholate	1.3	2.3	2.2	6.4	0, 0.2, 0, 0.4	1.65, 1.78
10% + oleic acid 5%					Average 0.15	1.71

¹ We are indebted to Prof. Forssell, Prof. Palmgren and Dr Dolk at the Veterinary High-school of Stockholm for their kindness in helping us to carry out this experiment.

chloroform were used. The lipid content of the lymph was determined by extraction with alcohol-ether (3:1), evaporating and weighing. The results are shown in Table III.

Even the horse lymph proved to be absolutely free from cholic acids after the injection into the intestine, in spite of the fact that the lipid value was fairly high, and though the bile acids were evidently increased in the portal blood.

DISCUSSION.

In a paper which will soon appear we propose, together with Jungner, to report experiments which show that even large amounts of bile acids injected into a peripheral vein of a healthy animal disappear from the blood almost immediately. If the acids are injected into a vein of the portal system the content even in heart blood is markedly higher.

For this reason we may suppose that if the bile acids were resorbed only by the lymph vessels and carried to the peripheral blood, we would scarcely have found any rise at all in the blood content. If they were resorbed by the portal vein, however, we might have found an increase in the portal and possibly also in the peripheral blood. The latter is indeed the case, as Table I shows, and the increase corresponds to a much higher resorption than would appear from a superficial estimate. Schwiegk [1932] has shown that the velocity of flow in the portal vein can be increased more than 200 %, for instance by cooling or by the presence of (especially fat) food in the intestines. Even a rise in the blood bile acids increases this velocity, which of course must again decrease the cholic acid content.

This does not exclude the possibility that there is a simultaneous resorption by the lymph vessels. If however a bile salt solution is injected peripherally into an animal with the bile duct ligatured, there will appear a much larger and more prolonged increase of the blood bile acid content than in normal animals. The figures in Table II show that even in animals thus jaundiced the elevation of the bile acid content of the systemic blood is evidently lower than that of the portal blood after resorption of bile acids.

The final evidence that cholic acids are not resorbed by the lymph vessels is given by the analysis of the lymph samples from cows and a horse, where no cholic acid at all could be found, even after injection into the intestines of 200 g. Na glycocholate and during resorption of fats.

By the experiments related above we believe it to be demonstrated that the bile acids, when being resorbed, do not follow the fatty acids through the lymph vessels but diffuse into the portal blood and are carried to the liver. This means that the choleic acids must be decomposed into fatty and bile acids immediately after passing the epithelial layer of the mucosa, and that the two substances thus after the common resorption follow different paths.

This may also have a clinical interest for bile acid therapy which is now frequently used. When the bile acids are given *per os* they will probably never appear in the peripheral blood if the liver is undamaged, whilst in certain cases of liver injury they may possibly be found there in a low concentration.

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