ON THE SECRETION OF BILE.

By SEIZABURO OKADA, M.D. (*Tokyo*).

(*From the Institute of Physiology, University College, London.*)

Introduction. All the experiments recorded in this paper were carried out on dogs, and the operations on them were performed for me by Professor Starling. The animals were provided with a permanent fistulous opening into the gall-bladder, the common bile-duct being ligatured, so that the total secretion of bile passed out by the fistula. In order to measure the secretion of bile, the dogs were slung and a rubber tube inserted in the fistula. As has already been noted by previous workers, the secretion is sometimes larger during the first hour of the observed period. This is possibly due to such factors as the excitement of the dogs before being slung, the retention of bile in the bile-ducts, remnants of food in the stomach from the last meal, or irritation caused by the introduction of the rubber tube. These possibilities were excluded as far as possible.

1. *The effect of diets of bread, butter and meat.*

The literature on this subject contains most contradictory statements. Nasse and Ritter(1) showed that a carbohydrate diet provokes a smaller secretion of bile than a meat diet, and that the addition of fat to a small quantity of meat increases the secretion but has no influence when added to a large quantity. Bidder and Schmidt(2) found that in cats on a continued diet of meat the secretion was greatly increased, while a pure fat diet diminished the secretion to the starvation level. Prévost and Binet(3), on the other hand, found that fresh butter, in quantities of 37 gms., had no influence on the amount of bile secreted. Rosenberg(4) stated that fat had a greater excitatory effect on the secretion than protein and carbohydrate. In his experiments on dogs he found that the secretion of bile after a meal of 250–500 gms. of horse-flesh and 125–500 gms. of rice or 60 gms. of bread was smaller than after the introduction of 50–120 gms. of olive oil into the stomach by means of the stomach-tube. Barbéra(5) found that

the secretion of bile is greatest on a protein diet, rather less on a fat diet, and insignificant on a carbohydrate diet (ingestion of cane sugar). On a mixed diet the secretion of bile varied according to the proportions of protein and fat contained in the diet. This author states that the duration of the secretion is longest on a fat diet, rather shorter on a meat diet, and very short on a carbohydrate diet. On a mixed diet the secretion was of longer or shorter duration, according to the amount of fat and protein present. According to Doyon(6) neither oil nor a mixture of oil and bile, introduced into the stomach, stimulates the secretion of bile as measured during the nine hours or twenty-four hours following administration. Fleig(7), on the other hand, observed in a chloralised dog an acceleration of the secretion after the injection of oil into the duodenum.

Many authors are of the opinion that the mechanism by which bile is secreted when it is required in the intestine, is mainly humoral. Rutherford(8) found dilute nitro-hydrochloric acid to be a hepatic stimulant of considerable power. Wertheimer(9) concluded from the researches of Dubois that the injection of acid into the duodenum or into the upper part of the jejunum stimulates the secretion of bile. Bayliss and Starling(10) found that the intravenous injection of a solution of secretin, entirely freed from bile salts, produced an immediate increase in the secretion of bile, and they observed that it would be appropriate if the mechanism involved in the increased production were identical with that responsible for the secretion of pancreatic juice. Fleig(7) concluded that the increase in the secretion of bile consequent on the introduction of acid into the intestine was due not only to a humoral effect but also in part to a nervous reflex. He concluded further that in the case of fats no hormone acting upon the liver is produced and believed their effect was entirely reflex.

In my experiments I first tried the effect of bread, butter and meat on the secretion of bile. In order that the same conditions of nourishment should obtain at the beginning of each experiment, each animal was given a regular diet prior to the morning of the experiment. Dog *A* received 300 gms. of horse-flesh daily, and Dog *B* 200 gms. of bread and 200 c.c. of milk.

The diets chosen for the experiments were of equal caloric value. The effect of small quantities of food was tried on Dog *A*, who received 40 gms. of bread, 14 gms. of butter, or 64 gms. of horse-flesh, while dog *B* received the larger amounts of 200 gms. of bread, 68 gms. of butter, or 320 gms. of horse-flesh. Immediately after the ingestion of any

one of these foods there was, as Barbéra observed, a diminution or cessation in the secretion of bile, after which there was a rapid increase which reached its maximum in the first or second hour of the experiment. In their initial effect on the secretion these foods differed little from each other, but after a meal of bread the diminution set in sooner than after butter or meat. With increase in the secretion there is apparently in every case a corresponding diminution in the solids present in the bile.

Details of these experiments will be seen from the following tables. Dog *A* (6 kilos) was operated on Oct. 20, 1914, and fed daily with 300 gms. of horse-flesh. Its weight remained practically constant throughout the period of observation. This dog died on Dec. 31, 1914. Dog *B* (6·8 kilos) was operated on Jan. 7, 1915, remaining under observation until March 1, 1915. It received a daily diet of 200 gms. of bread and 200 c.c. of milk during the course of the experiments with bread, butter and meat. It was afterwards fed on horse-flesh.

TABLE I. *Dog A. The effect of feeding with* 40 *gms. of bread.*

	31. 10. 14		16. 11. 14		18. 11. 14		Average	
	Bile c.c.	Solids gms. in 1 c.c.	Bile c.c.	Solids gms. in 1 c.c.	Bile c.c.	Solids gms. in 1 c.c.	Bile c.c.	Solids gms. in 1 c.c.
Fasting	2·8	·074	2·8	·124	3·0	·101	2·9	·100
1 hr. after feeding	4·0	·062	6·2	·092	3·9	·099	4·7	·085
2 „ „ „	6·0	·030	5·6	·048	5·7	·059	5·8	·045
3 „ „ „	4·3	·034	4·3	·051	4·7	·058	4·4	·048
4 „ „ „	3·3	·034	2·9	·067	4·6	·050	3·6	·050
5 „ „ „	2·3	·035	1·7	·079	4·3	·048	2·8	·051
6 „ „ „	2·9	·035	3·0	·086	4·0	·047	3·3	·055

TABLE II. *Dog A. The effect of feeding with* 14 *gms. butter.*

	2. 11. 14		6. 11. 14		11. 11. 14		Average	
Fasting	2·5	·089	2·0	·103	2·3	·066	2·3	·084
1 hr. after feeding	6·1	·056	6·0	·066	5·8	·052	6·0	·057
2 „ „ „	5·0	·033	6·8	·033	6·1	·053	6·0	·040
3 „ „ „	3·7	·035	5·7	·030	4·2	·055	4·5	·039
4 „ „ „	3·4	·039	4·6	·033	3·5	·062	3·8	·044
5 „ „ „	4·0	·034	4·0	·035	3·4	·069	3·8	·045
6 „ „ „	3·6	·030	3·4	·038	3·0	·064	3·3	·043

TABLE III. *Dog. A. The effect of feeding with* 64 *gms. boiled horse-flesh.*

	4. 11. 14		9. 11. 14		13. 11. 14		Average	
Fasting	2·7	·052	2·8	·061	3·6	·090	3·0	·070
1 hr. after feeding	5·2	·049	5·0	·048	5·2	·083	5·1	·060
2 „ „ „	4·4	·038	5·2	·037	5·1	·062	4·9	·046
3 „ „ „	4·0	·030	4·9	·049	4·7	·077	4·5	·053
4 „ „ „	4·2	·031	2·8	·067	3·0	·076	3·3	·055
5 „ „ „	3·8	·031	2·5	·070	2·3	·085	2·9	·057
6 „ „ „	3·2	·031	3·6	·055	2·8	·073	3·2	·052

TABLE IV. *Dog A. Averages of the diets of bread, butter and horse-flesh.*

	Bread		Butter		Meat	
	Bile c.c.	Solid gms. in 1 c.c.	Bile c.c.	Solid gms. in 1 c.c.	Bile c.c.	Solid gms. in 1 c.c.
Fasting	2·9	·100	2·3	·084	3·0	·070
1 hr. after feeding	4·7	·085	6·0	·057	5·1	·060
2 „ „ „	5·8	·045	6·0	·040	4·9	·046
3 „ „ „	4·4	·048	4·5	·039	4·5	·053
4 „ „ „	3·6	·050	3·8	·044	3·3	·055
5 „ „ „	2·8	·051	3·8	·045	2·9	·057
6 „ „ „	3·3	·055	3·3	·043	3·2	·052

TABLE V. *Dog B. The effect of feeding with* 200 *gms. bread.*

	18. 1. 15		25. 1. 15		Average	
	Bile	Solids	Bile	Solids	Bile	Solids
Fasting	3·1	·053	3·4	·062	3·3	·058
1 hr. after feeding	8·0	·051	8·2	·045	8·1	·048
2 „ „ „	9·0	·026	8·4	·036	8·7	·031
3 „ „ „	6·8	·027	6·9	·034	6·9	·031
4 „ „ „	6·1	·027	4·8	·035	5·5	·031
5 „ „ „	5·7	·030	3·3	·034	4·5	·031
6 „ „ „	4·8	·029	3·8	·034	4·3	·031
7 „ „ „	4·6	·028	4·2	·034	4·4	·031

TABLE VI. *Dog B. The effect of feeding with* 68 *gms. butter.*

	22. 1. 15		27. 1. 15		Average	
	Bile	Solids	Bile	Solids	Bile	Solids
Fasting	2·6	·049	3·5	·048	3·1	·048
1 hr. after feeding	7·2	·047	7·3	·040	7·3	·043
2 „ „ „	8·8	·038	7·8	·030	8·3	·034
3 „ „ „	8·2	·039	6·4	·033	7·3	·036
4 „ „ „	7·1	·040	5·2	·026	6·2	·034
5 „ „ „	6·8	·036	4·3	·030	5·6	·034
6 „ „ „	5·9	·037	5·1	·028	5·5	·033
7 „ „ „	5·4	·037	4·5	·031	5·0	·034

TABLE VII. *Dog B. The effect of feeding with* 320 *gms. boiled horse-flesh.*

	16. 1. 15		20. 1. 15		Average	
	Bile	Solids	Bile	Solids	Bile	Solids
Fasting	3·1	·061	4·2	·035	3·7	·046
1 hr. after feeding	8·5	·047	7·1	·027	7·8	·038
2 „ „ „	7·4	·026	7·3	·026	7·3	·026
3 „ „ „	6·2	·026	6·3	·027	6·3	·027
4 „ „ „	6·0	·026	6·3	·025	6·2	·025
5 „ „ „	6·0	·026	7·0	·029	6·5	·028
6 „ „ „	6·2	·029	4·8	·029	5·5	·029
7 „ „ „	5·6	·028	6·2	·029	5·8	·029

TABLE VIII. *Dog B. Averages of diets of bread, butter and horse-flesh.*

	Bread		Butter		Meat	
	Bile c.c.	Solids gms. in 1 c.c.	Bile c.c.	Solids gms. in 1 c.c.	Bile c.c.	Solids gms. in 1 c.c.
Fasting	3·3	·058	3·1	·048	3·7	·046
1 hr. after feeding	8·1	·048	7·3	·043	7·8	·038
2 „ „ „	8·7	·031	8·3	·034	7·3	·026
3 „ „ „	6·9	·031	7·3	·036	6·3	·027
4 „ „ „	5·5	·031	6·2	·034	6·2	·025
5 „ „ „	4·5	·031	5·6	·034	6·5	·028
6 „ „ „	4·3	·031	5·5	·033	5·5	·029
7 „ „ „	4·4	·031	5·0	·034	5·8	·029

2. *The effect of starvation.*

It is well known that in starvation the quantity of bile secreted is diminished and the concentration increased. Rosenberg observed that the secretion of bile in animals receiving a regular diet was still increased at the usual hour even though no food or drug had been administered. Albertoni and Barbéra(5) found that though the amount of bile secreted during starvation diminishes, there is never an entire cessation of secretion even up to the time of the death of the animal. These observers were not able to confirm the statement of Rosenberg. My observations on this point are in accordance with those of Albertoni and Barbéra. Moreover I noted that the excitatory effect of taking food on the liver cells was diminished during starvation.

The results of this series of observations are given in the following tables. The dogs were kept in cages and received no food the day before the experiment except water. They were thus in a state of temporary starvation.

TABLE IX. *Dog A. The effect of food after temporary starvation.*

	Bread 79 gms. Biscuits 41 gms. 20. 11. 14		Horse-flesh 204 gms. 23. 11. 14		Butter 44 gms. 25. 11. 14	
	Bile c.c.	Solids gms. in 1 c.c.	Bile c.c.	Solids gms. in 1 c.c.	Bile c.c.	Solids gms. in 1 c.c.
Fasting	2·0	·109	0·8	·144	2·5	·063
1 hr. after feeding	3·6	·105	2·8	·107	2·7	·045
2 „ „ „	4·3	·047	3·6	·044	3·8	·025
3 „ „ „	3·1	·053	3·8	·031	3·6	·021
4 „ „ „	1·9	·066	3·0	·038	1·2	·024
5 „ „ „	0·9	·097	2·2	·044	1·7	·024
6 „ „ „	1·4	·091	2·1	·052	1·0	—

Dog's weight on 20. 11. 14 = 5·5 kilos.
„ „ „ 23. 11. 14 = 5·3 „
„ „ „ 25. 11. 14 = 5·2 „

TABLE X. *Dog B. The effect of food after temporary starvation.*

	Bread 200 gms. 5. 2. 15		Butter 68 gms. 8. 2. 15		Horse-flesh 320 gms. 10. 2. 15	
	Bile c.c.	Solids gms. in 1 c.c.	Bile c.c.	Solids gms. in 1 c.c.	Bile c.c.	Solids gms. in 1 c.c.
Fasting	1·3	·048	1·5	·044	1·4	·048
1 hr. after feeding	4·1	·039	5·2	·032	2·1	·048
2 „ „ „	5·3	·029	6·1	·023	2·9	·049
3 „ „ „	4·6	·031	5·4	·027	2·8	·044
4 „ „ „	4·5	·029	4·8	·026	2·9	·046
5 „ „ „	3·3	·029	3·0	·030	1·8	·047
6 „ „ „	3·4	·028	3·3	·032	1·6	·041
					Diarrhœa	

Dog's weight on 5. 2. 15 = 5·95 kilos.
„ „ „ 8. 2. 15 = 6·00 „
„ „ „ 10. 2. 15 = 5·90 „

3. *The effect of protein, carbohydrate and fat.*

White of egg was chosen for the experiments on the influence of protein on the secretion of bile, on account of the fact that its constituents other than protein are present in such small quantities as to be almost negligible. In some experiments carried out by Brüno and Klodnizki(11) it was observed that no bile at all was expelled from the Pawlow's fistula after the introduction of raw white of egg into the empty stomach. When, however, the digestion of the white of egg is allowed to proceed in consequence of the secretion of gastric juice, evoked either chemically or psychically, the usual secretion of bile takes place. The ingestion of heat-coagulated white of egg always results in a secretion of bile.

The results of my experiments are as follows:

Dog C (10–11 kilos) was operated on Jan. 7, 1915, and fed daily with 400 gms. of horse-flesh. It died on April 22 as the result of an accident.

Dog D (5·7 kilos) was operated on April 6, 1915, and fed daily with 300 gms. of horse-flesh. This dog was killed on June 4.

Dog E (6·5 kilos) was operated on April 29, 1915, and fed daily with 300 gms. of horse-flesh.

TABLE XI. *Dog C.* Introduction of 200 c.c. raw white of egg. 31. 3. 15.

	Bile c.c.	Solids gms. in 1 c.c.
1st hour (fasting)	3·5	·065
2nd hour „	3·0	·062
1st hour after introduction	3·3	·038
2nd „ „ „	5·1	·040
3rd „ „ „	3·2	·043
4th „ „ „	3·8	·041

TABLE XII. *Dog D.* Introduction of 400 c.c. raw white of egg. 6. 6. 15.

	Bile c.c.	Solids gms. in 1 c.c.
1st hour (fasting)	3·1	·070
2nd „ „	3·6	·066
1st hour after introduction	4·2	·062
2nd „ „ „	3·7	·055
3rd „ „ „	3·9	·055
4th „ „ „	3·2	·051

TABLE XIII. *Dog E.* Introduction of 200 c.c. of raw white of egg. 27. 5. 15.

1st hour (fasting)	3·4	·062
2nd hour „	4·1	·059
1st hour after introduction	6·2	·036
2nd „ „ „	8·0	·033
3rd „ „ „	6·1	·034
4th „ „	4·0	·037

TABLE XIV. *Same dog.* Ingestion of 150 c.c. boiled white of egg with 10 gms. of cane sugar. 22. 5. 15.

1st hour (fasting)	3·7	·062
2nd „ „	3·0	·065
1st hour after introduction	4·4	·035
2nd „ „ „	7·4	·034
3rd „ „ „	6·6	·038
4th „ „ „	5·3	·038

The variability in the increase of the secretion after the introduction of raw white of egg is probably caused by differences in the degree of digestion occurring in the stomach. The result of one experiment with boiled white of egg is given in Table XIV. The introduction of cane sugar into the stomach results in no change or a slight diminution in the secretions.

TABLE XV. *Dog C.* Introduction of 50 gms. of cane sugar dissolved in 200 c.c. of water. 12. 4. 15.

	Bile c.c.	Solids gms. in 1 c.c.
1st hour (fasting)	2·4	·062
2nd „ „	2·5	·056
1st hour after administration	2·4	·053
2nd „ „ „	2·3	·053
3rd „ „ „	2·3	·055
4th „ „ „	2·1	·054

TABLE XVI. *Dog D.* 29. 4. 15.

	Bile c.c.	Solid gms. in 1 c.c.
1st hour (fasting)	2·4	·061
2nd „ „	2·6	·060
1st hour after administration	1·7	·072
2nd „ „ „	1·2	·076
3rd „ „ „	1·8	·071
4th „ „ „	1·6	·070

TABLE XVII. *Dog E.* 14. 6. 15.

1st hour (fasting)	4·1	·058
2nd „ „	3·6	·060
1st hour after administration	3·2	·061
2nd „ „ „	2·4	·066
3rd „ „ „	2·8	·066

In Table XVIII is given the result of feeding with baked starch. The effect on the secretion of the bile was insignificant.

TABLE XVIII. *Dog C.* Ingestion of well-baked starch (100 gms.) (+ 5 gms. of cane sugar). 29. 3. 15. The dog ate this greedily for 20 minutes.

	Bile c.c.	Solids gms. in 1 c.c.
1st hour (fasting)	2·5	·069
2nd „ „	2·6	·065
1st hour after ingestion	4·2	·048
2nd „ „ „	3·5	·046
3rd „ „ „	3·0	·051
4th „ „ „	3·2	·053

The statements as to the effect of oil and fat on the secretion of bile are conflicting, many authors having found them to have a stimulating effect on the secretion, while others state them to be without effect. I therefore made careful experiments on this point. In many cases fat proved an efficient stimulant, but often only a slight increase occurred and occasionally negative results were obtained. These negative results were especially noticeable in dogs with long-standing fistulæ. In these dogs diarrhœa was often present after the ingestion of fat or oil, though they were in other respects quite healthy. It is possible therefore that their ability to digest fat may have been impaired. The following tables show the positive results of fat ingestion.

TABLE XIX. *Dog C.* Introduction of 100 c.c. of olive oil. 9. 2. 15.

	Bile c.c.	Solids gms. in 1 c.c.
1st hour (fasting)	4·1	·070
2nd „ „	3·8	·069
1st hour after introduction	6·1	·043
2nd „ „ „	9·8	·032
3rd „ „ „	8·6	·031
4th „ „ „	7·0	·031
5th „ „ „	7·1	·032

TABLE XX. *Dog D.* Introduction of 100 c.c. olive oil. 23. 4. 15.

1st hour (fasting)	2·7	·082
2nd „ „	2·9	·079
1st hour after introduction	5·2	·051
2nd „ „ „	7·1	·043
3rd „ „ „	7·3	·042
4th „ „ „	6·4	·042
5th „ „ „	4·2	·044

TABLE XXI. *Dog E.* Introduction of 100 c.c. olive oil. 14. 5. 15.

1st hour (fasting)	5·5	·057
2nd „ „	5·3	·058
1st hour after introduction	7·1	·047
2nd „ „ „	7·9	·042
3rd „ „ „	6·4	·041
4th „ „ „	6·6	·042

4. *The effect of acids on the secretion of bile.*

Most of the researches which have been carried out on the effect of acids on the secretion of bile have been made on animals under anæsthesia in whom a temporary fistula has been established. I thought it worth while therefore to observe the effect on animals provided with a permanent fistula.

TABLE XXII. *Dog A.* Feeding with 200 c.c. 0·4 % HCl solution.

	27. 11. 14		30. 11. 14	
	Bile c.c.	Solids gms. in 1 c.c.	Bile c.c.	Solids gms. in 1 c.c.
1st hour (fasting)	3·2	·044	3·1	·075
2nd „ „	3·4	·041	2·8	·070
1st hour after feeding	9·0	·037	9·8	·034
2nd „ „ „	6·9	·030	7·6	·032
3rd „ „ „	1·7	·034	4·2	·048
4th „ „ „	3·1	·030	4·5	·050
5th „ „ „	—	—	3·4	·050

TABLE XXIII. *Dog C.* Introduction of 200 c.c. of 0·4 % HCl solution. 26. 1. 15.

	Bile c.c.	Solids gms. in 1 c.c.
1st hour (fasting)	4·3	·050
2nd „ „	3·8	·051
1st hour after introduction of acid	13·3	·026
2nd „ „ „ „	5·7	·028
3rd „ „ „ „	3·0	·031

TABLE XXIV. *Dog C.* Introduction of 200 c.c. 0·5 % lactic acid solution. 2. 2. 15.

1st hour (fasting)	2·8	·065
2nd „ „	2·6	·061
1st hour after introduction of acid	7·3	·030
2nd „ „ „ „	4·9	·034
3rd „ „ „ „	3·7	·036

TABLE XXV. In these experiments the secretion was measured every 15 minutes after the feeding of 200 c.c. 0·4 % HCl solution.

½ hours	Dog *A* 30. 11. 14 Bile c.c.		Dog *C* 26. 1. 15 Bile c.c.	
1st	1·7		2·6	
2nd	3·2	= 9·8	3·9	= 13·3
3rd	2·6		3·7	
4th	2·3		3·1	
5th	2·3		2·7	
6th	2·2	= 7·6	2·0	= 5·7
7th	1·8		0·8	
8th	1·3		0·2	

It will be seen from these tables that the secretion of bile after ingestion of acid reaches its maximum during the first hour, decreasing markedly in the second hour, at the end of which it almost returns to the amount during fasting. The course of the secretion in this case is very similar to that of the pancreatic secretion observed by Walter(12) in his experiments.

The stimulating effect of acids on the expulsion of bile was first observed by Claude Bernard(13), who placed a drop of acid in the mouth of the common bile-duct and observed an immediate gush of bile into the intestine. This observation was confirmed some years after by Küthe(14); Brüno(11), on the other hand, found that the introduction of hydrochloric acid into the duodenum of dogs provided with a Pawlow fistula was not followed by any flow of bile, and he concluded that acids did not act as stimuli for the expulsion of bile. But, as Fleig has already shown, it is possible that in the operative

procedures necessary for the preparation of the fistula, the nervous connections of the duct sphincter are cut, so that the conditions are not the same as they would be in the intact animal. In order to test this point I made three experiments on dogs anæsthetised with A.C.E. mixture; an opening in the duodenum was made so that the orifice of the common bile-duct could be clearly observed. 0·4 % hydrochloric acid or 0·5 % lactic acid was then introduced into the lower part of the duodenum. In each case this was followed in two or three minutes by a rapid flow of bile into the intestine. The same result was obtained in an experiment in which all the hepatic ducts were ligatured, so that the gall-bladder was only connected with the common bile-duct. From these results it is concluded that acids introduced into the duodenum stimulate not only the secretion but also the expulsion of bile into the intestine.

5. *The effect of secretin.*

In the course of their experiments on pancreatic secretion, Bayliss and Starling(10) tried the effect of secretin on the secretion of bile. They pointed out that as the secretion of bile is very much influenced by the blood-pressure, the depressor substance in the ordinary secretin preparation would probably obscure any excitatory effect of the secretin itself, and, on the other hand, the bile-salts in the preparation would increase the rate of secretion of bile. They therefore made use of a purified preparation, free from bile-salts and containing only a small amount of depressor substance. The injection of this preparation into the veins of an animal provided with a temporary fistula caused the rate of secretion to be almost doubled. Fleig noted that the intravenous injection into a chloralised dog of the blood from an isolated loop of duodeno-jejunum, into which a solution of 0·5 % hydrochloric acid had been introduced, caused a similar increase in the rate of secretion.

The secretin used in my experiments was prepared by the method devised by Wertheimer(15) and elaborated by Matsuo(16) which is as follows. The pylorus, bile-duct and pancreatic duct having been ligatured, the lumen of the duodenum was thoroughly washed out with normal saline and a 0·4 % solution of hydrochloric acid introduced into it. After an interval of five minutes the duodenal contents were removed, boiled, neutralised and filtered.

Matsuo found that this preparation caused only a slight fall of blood-pressure but that it had a marked effect on the pancreatic

secretion. I confirmed this statement in a dog provided with temporary biliary and pancreatic fistulæ, and I noted also that the secretion of bile was almost doubled. The results obtained on dogs with permanent fistulæ are as follows.

TABLE XXVI. *Dog A.* Injection of 10 c.c. of secretin solution into the right median vein. The bile was measured every 15 minutes. 2. 12. 14.

		Bile c.c.		Solids gms. in 1 c.c.
1st ¼-hour (fasting)		0·9		
2nd ,,	,,	1·0	= 3·6	·068
3rd ,,	,,	1·0		
4th ,,	,,	0·7		
1st ,,	after injection	1·8		
2nd ,,	,,	1·6	= 6·2	·058
3rd ,,	,,	1·4		
4th ,,	,,	1·4		
5th ,,	,,	1·3		
6th ,,	,,	1·3	= 4·1	·047
7th ,,	,,	0·9		
8th ,,	,,	0·6		
9th ,,	,,	0·7		
10th ,,	,,	0·7	= 2·7	·069
11th ,,	,,	0·7		
12th ,,	,,	0·6		

TABLE XXVII. *Dog A.* No food given on the day preceding the experiment. Injection of 10 c.c. of secretin solution into the femoral vein. 7. 12. 14.

1st ¼-hour (fasting)		0·6		
2nd ,,	,,	0·7	= 2·3	·081
3rd ,,	,,	0·6		
4th ,,	,,	0·4		
1st ,,	after injection	1·6		
2nd ,,	,,	1·0	= 4·2	·050
3rd ,,	,,	0·8		
4th ,,	,,	0·8		
5th ,,	,,	0·9		
6th ,,	,,	1·0	= 2·7	·045
7th ,,	,,	0·5		
8th ,,	,,	0·3		
9th ,,	,,	0·5		
10th ,,	,,	0·9	= 3·0	·057
11th ,,	,,	0·9		
12th ,,	,,	0·7		

TABLE XXVIII. *Dog C.* Injection of secretin. 28. 1. 15.

	Bile c.c.		Solids gms. in 1 c.c.
1st ¼-hour (fasting)	0·8		
2nd „ „	1·2	= 4·1	·050
3rd „ „	0·9		
4th „ „	1·2		
Injection of 10 c.c. of secretin into right femoral vein.			
1st ¼-hour	1·7		
2nd „	1·0	= 4·4	·053
3rd „	0·9		
4th „	0·8		
Injection of 20 c.c. secretin into left femoral vein.			
1st ¼-hour	2·6		
2nd „	1·2	= 5·9	·045
3rd „	1·0		
4th „	1·1		

It will be seen that the increased secretion is marked only during the first quarter of an hour. Special precautions were therefore taken to avoid any retention of bile and any other exciting influence on its secretion. That the effect was due to other possible contents of the solution, such as bile-salts or peptone, may be excluded, in view of the fact that the secretin, if kept in the cold store and injected on the following day, had no influence on the secretion of bile, the preparation soon losing its power in a neutral solution.

6. *The effect of peptone and extract of meat.*

Peptone. It was observed by Asher and Barbéra(17) that the intravenous injection of peptone into a dog provided with a permanent fistula caused a considerable increase in the flow of bile. Prévost and Binet(3) also state that the secretion is almost doubled by the introduction of 15 gms. of peptone into the stomach. Doyon(6), on the other hand, showed that peptone inhibits the secretion of bile and provokes a strong contraction of the gall-bladder. Fleig concludes from his experiments that the action of peptone injected into the intestine on the liver is reflex, and he states that this reflex must be secretory in nature since the effect of the peptone was more noticeable after the ligature of the cystic canal. My results in this connection are as follows:

TABLE XXIX. *Dog C.* Introduction into the stomach of a boiled solution of 10 gms. of Witte's peptone in 150 c.c. of water. 10. 3. 15.

	Bile c.c.	Solids gms. in 1 c.c.
1st hour (fasting)	3·7	·072
2nd „ „	3·2	·067
Introduction of peptone.		
1st hour	3·7	·041
2nd „	8·4	·034
3rd „	3·5	·041

TABLE XXX. *Dog D.* Same exp. 21. 4. 15.

1st hour (fasting)	4·0	·078
2nd „ „	3·5	·077
Introduction of peptone.		
1st hour	2·7	·060
2nd „	12·6	·040
3rd „	5·9	·041

TABLE XXXI. *Dog.* 7 kilos. Morphia and A.C.E. mixture. Cannula inserted in the common bile-duct and the cystic duct ligated. Injection into the femoral vein of 30 c.c. of 10 % Witte's peptone dissolved in normal saline solution. The outflow was recorded with the drop recorder.

	Intervals in seconds between each drop
Before injection	115, 117
After injection	430, 280, 115, 55, 55, 55, 50, 50, 40, 40

After the introduction of peptone into the stomach no flow of bile occurred for 30 minutes. There was also a considerable interval between the intravenous injection of peptone and the first drop of bile, due perhaps to the lowering of the blood-pressure. In both cases however there is a marked increase in the secretion, and it seems justifiable to conclude that a humoral mechanism is concerned in the action of peptone, although the experiments do not preclude the possibility of its action being also a reflex one.

Extract of meat. Liebig's extract (7·5–10 %) was found by Brüno(11) in experiments with Pawlow's fistula to cause an expulsion of bile, though to a less extent than other stimulants. This excitatory effect was however denied by Klodnizki(11). According to Fleig, the injection of Liebig's extract into the rectum or into the blood produces no acceleration in the secretion of bile, nor do extracts of stomach or intestine mucosa made with a solution of Liebig's extract.

Fleig also obtained negative results by intravenous injection of the returning blood from the duodenum, into which the solution had been previously injected. The results of my experiments are as follows:

TABLE XXXII. *Dog A.* The effect of the introduction of 200 c.c. of a 10 % solution of Liebig's extract into the stomach. 5. 12. 15.

	Bile c.c.	Solids gms. in 1 c.c.
1st hour (fasting)	3·1	·050
2nd „ „	3·2	·049
Introduction of extract.		
1st hour	11·2	·047
2nd „	7·3	·048
3rd „	3·6	·041
4th „	1·8	·031
5th „	4·5	·030

TABLE XXXIII. *Dog C.* The dog was not fed the day before the experiment. Introduction of 200 c.c. of a 10 % solution of Liebig's extract into the stomach. 13. 2. 15.

1st hour (fasting)	4·8	·079
2nd „ „	4·5	·076
Introduction of extract.		
1st hour	5·7	·065
2nd „	6·2	·030
3rd „	4·1	·032

These experiments show that meat extract introduced into the stomach acts as a very powerful cholagogue, the action probably being partly due to the acid in the gastric juice secreted as a result of the introduction of the meat extract.

7. *The effect of introduction of water, sodium bicarbonate and soap.*

Water. Rutherford(8) and many other subsequent workers found that the introduction of water into the duodenum or into the stomach gives rise to practically no increase in the rate of bile secretion, and the experiments given in the following tables fully bear out their conclusions.

TABLE XXXIV. *Dog A.* Introduction of 200 c.c. cold water. 12. 12. 14.

	Bile c.c.	Solids gms. in 1 c.c.
1st hour (fasting)	3·9	·066
2nd „ „	3·6	·067
1st hour after introduction	4·0	·055
2nd „ „ „	3·2	·057
3rd „ „ „	3·3	·057

TABLE XXXV. *Dog C.* Introduction of 200 c.c. cold water. 11. 2. 15.

	Bile c.c.	Solids gms. in 1 c.c.
1st hour (fasting)	3·5	·071
2nd „ „	3·2	·070
1st hour after introduction	3·9	·068
2nd „ „ „	3·7	·068
3rd „ „ „	3·1	·065

TABLE XXXVI. *Dog C.* Introduction of 300 c.c. warm water (40° C.). 9. 4. 15.

1st hour (fasting)	3·3	·076
2nd „ „	2·8	·077
1st hour after introduction	4·4	·061
2nd „ „ „	3·0	·068
3rd „ „ „	1·5	·070

Sodium bicarbonate. Various workers have found that sodium bicarbonate has no effect as a bile stimulant, though Prévost and Binet believed they had demonstrated a slight increase of bile after the introduction of sodium bicarbonate into the stomach. The following experiments seem to indicate that it is practically without influence.

TABLE XXXVII. *Dog A.* Introduction of 200 c.c. of 1 % solution of sodium bicarbonate. 15. 12. 14.

	Bile c.c.	Solids gms. in 1 c.c.
1st hour (fasting)	2·7	·091
2nd „ „	2·5	·090
1st hour after introduction	2·9	·086
2nd „ „ „	2·6	·084
3rd „ „ „	2·4	·088

TABLE XXXVIII. *Dog C.* Introduction of 200 c.c. of 1·5 % sodium bicarbonate solution. 8. 3. 15.

1st hour (fasting)	2·0	·089
2nd „ „	3·6	·067
1st hour after introduction	4·4	·058
2nd „ „ „	2·4	·061
3rd „ „ „	1·7	·079

Soap. According to Doyon, soap causes if anything, a slight diminution in the bile secretion during the first 9 and 24 hours, but the following experiments seem to indicate that for four hours at any rate after ingestion it acts as quite a powerful stimulus.

TABLE XXXIX. *Dog D.* Feeding of 100 c.c. 3 % sodium oleate. 27. 4. 15.

	Bile c.c.	Solids gms. in 1 c.c.
1st hour (fasting)	4·9	·057
2nd „ „	4·0	·056
1st hour after feeding	4·5	·041
2nd „ „ „	6·6	·038
3rd „ „ „	8·6	·039
4th „ „ „	7·3	·038

TABLE XL. *Dog E.* Feeding of 100 c.c. of 3 % sodium oleate.

1st hour (fasting)	4·8	·072
2nd „ „	3·9	·072
1st hour after ingestion	6·2	·044
2nd „ „ „	5·4	·042
3rd „ „ „	9·9	·034
4th „ „ „	7·6	·034

8. *The effect of bile, bile-salts and hæmoglobin.*

It has long been known that bile itself is a very powerful stimulant of the secretion of bile. Many authors have proved this by the intravenous injection of bile-salts or their introduction into the stomach. Schiff(18), and later Rosenberg(4), observed that the introduction of bile into the alimentary canal caused not only an increase in the secretion of bile but also, unlike other cholagogues which yield a diluted bile, an increase in its concentration. In two cases I also observed an increase in the quantity and concentration of bile, while the pigment content was diminished. This is perhaps due to the fact that the bile-salts are principally absorbed into the blood vessels and eliminated by the liver, while the pigments, once excreted, are almost entirely lost with the fæces. Investigators who have studied the effect of bile differ in their interpretation of the cholagogue effects of bile and bile-salts. Thus Schiff believed that the bile is absorbed and re-excreted as a whole, that is, there was a circulation of bile between the liver and intestines. Socoloff(19) believed that the liver was incapable of re-secreting bile which had been once secreted and absorbed into the blood vessels. He pointed out that if any tissue becomes impregnated with biliary constituents, it would be easy for this tissue, if a gland, to pass these constituents out into a secretion from which they were normally absent, and it seems likely that the increased secretion of

bile under these circumstances in the liver is due to similar mechanical conditions, so that when the blood is charged with biliary constituents, more of them appear in the biliary secretion. Rosenberg however pointed out that if this were the case, it would be difficult to explain the increased concentration of bile which is observed. My results are as follows:

TABLE XLI. *Dog A.* Introduction of 50 c.c. dog's bile into the stomach. 9. 12. 14.

	Bile c.c.	Solids gms. in 1 c.c.
1st hour (fasting)	2·7	·095
2nd „ „	2·5	·093
1st hour after administration	12·5	·096
2nd „ „ „	6·6	·109
3rd „ „ „	3·0	·119

TABLE XLII. *Dog C.* Introduction into the stomach of 50 c.c. ox bile (0·074 gms. solids in 1 c.c.). 29. 1. 15.

1st hour (fasting)	3·4	·050
2nd „ „	3·1	·051
1st hour after administration	14·7	·067
2nd „ „ „	15·6	·085
3rd „ „ „	12·0	·069
4th „ „ „	4·5	·087

TABLE XLIII. *Dog A.* The effect of bile-salts. Introduction of 1·5 gms. glycocholic acid and 0·5 gms. sodium bicarbonate in 50 c.c. of water into the stomach. 23. 12. 14.

1st hour (fasting)	3·9	·054
2nd „ „	3·8	·051
1st hour after administration	5·9	·107
2nd „ „ „	4·3	·056
3rd „ „ „	3·1	·048

TABLE XLIV. *Dog C.* Introduction of 3·0 gms. glycocholic acid and 2·0 gms. natrium bicarbonicum in 50 c.c. of water into the stomach. 22. 3. 15.

1st hour (fasting)	2·9	·065
2nd „ „	3·2	·062
1st hour after administration	7·3	·081
2nd „ „ „	5·1	·076
3rd „ „ „	3·8	·078

Since the actions of bile and pancreatic juice are to a great extent co-operative, it is not surprising that the flow of bile should run parallel

with that of pancreatic juice. When bile is introduced into the intestine of a dog provided with temporary biliary and pancreatic fistulæ, no secretion of pancreatic juice followed, although the flow of bile was decidedly increased. This is probably due to the fact that in this case the outflow of bile represents not a true secretion but an excretion of the toxic products which have been absorbed into the blood.

Hæmoglobin. According to Tarchanoff(20) and Vossius(21) the injection of bilirubin is followed by a marked increase in the excretion of bile pigments, and Tarchanoff and Stadelmann(22) also obtained the same result after injection of hæmoglobin, though Vossius was not able to confirm this. The two experiments which I have carried out support Tarchanoff's conclusion, the increase of bile pigments being obvious on inspection.

The hæmoglobin employed was a crystalline preparation made by the method of Hoppe-Seyler. 10 c.c. of the 10 % solution was given to dog *A* and 20 c.c. to dog *C*. In both cases there was a marked increase in the content of bile pigments without any remarkable alteration in the amount of solids or in the quantity of the bile.

9. *The effect of certain drugs regarded as cholagogues.*

(*a*) *Sodium salicylate.* This drug has been proved by Rutherford, Vignal and Doods and many other authors to be a powerful cholagogue, and my experiments confirm this fact.

TABLE XLV. *Dog C.* Administration of 2·0 gms. sodium salicylate dissolved in 100 c.c. water. 1. 3. 15.

	Bile c.c.	Solids gms. in 1 c.c.
1st hour (fasting)	3·3	·069
2nd „ „	3·2	·072
1st hour after administration	6·2	·063
2nd „ „ „	5·7	·027
3rd „ „ „	7·2	·025
4th „ „ „	5·3	·025

TABLE XLVI. *Dog B.* Under same conditions as the above. 23. 2. 15.

1st hour (fasting)	2·9	·052
2nd „ „	3·6	·048
1st hour after administration	6·3	·038
2nd „ „ „	6·0	·035
3rd „ „ „	6·8	·034
4th „ „ „	5·4	·034

(*b*) *Salol.* Prévost and Binet found salol to have a stimulating effect on the secretion of bile, but their results were not confirmed by Pfaff and Balch(23). My experiments showed a slight increase, as will be seen from the following tables.

TABLE XLVII. *Dog B.* 2·0 gms. salol boiled in 70 c.c. water and introduced after cooling into the stomach. 25. 2. 15.

	Bile c.c.	Solids gms. in 1 c.c.
1st hour (fasting)	2·6	·027
2nd „ „	2·6	·024
1st hour after administration	3·8	·021
2nd „ „ „	4·5	·021
3rd „ „ „	2·9	·020
4th „ „ „	3·4	·021

TABLE XLVIII. *Dog C.* 2·0 gms. salol boiled in 100 c.c. water and administered after cooling. 3. 3. 15.

1st hour (fasting)	3·5
2nd „ „	2·8
1st hour after administration	3·4
2nd „ „ „	3·6
3rd „ „ „	4·6
4th „ „ „	3·8

(*c*) *Calomel.* Out of four experiments carried out by Rutherford and Vignal with calomel, diminution in the secretion of bile occurred in three, while in one there was a slight increase. An occasional diminution has been observed by other authors but in no case has an increase been obtained. I also obtained a diminution.

TABLE XLIX. *Dog C.* 0·3 gm. calomel in 50 c.c. water introduced into the stomach. 24. 2. 15.

	Bile c.c.	Solids gms. in 1 c.c.
1st hour (fasting)	3·5	·081
2nd „ „	3·7	·078
1st hour after ingestion	3·8	·061
2nd „ „ „	3·2	·051
3rd „ „ „	2·7	·047
4th „ „ „	1·6	Diarrhœa

(*d*) *Cream of Tartar.* This drug was found by Petrowa(24) to have no effect on the secretion of bile. In two dogs however I obtained an increased secretion.

TABLE L. *Dog C.* Introduction of 5·0 gms. Cream of Tartar in 100 c.c. of water into the stomach. 26. 2. 15.

	Bile c.c.	Solids gms. in 1 c.c.
1st hour (fasting)	3·2	·061
2nd „ „	3·3	·060
1st hour after administration	5·1	·060
2nd „ „ „	4·1	·056
3rd „ „ „	4·7	·054
4th „ „ „	5·2	·049

TABLE LI. *Dog B.* 3·0 gms. Cream of Tartar in 100 c.c. of water. 27. 2. 15.

1st hour (fasting)	2·3	·030
2nd „ „	2·5	·029
1st hour after administration	4·1	·028
2nd „ „ „	5·5	·024
3rd „ „ „	4·3	·022
4th „ „ „	3·9	—

(*e*) *Chloral.* Gottlieb(25), Wertheimer and Lepage(26), and others have demonstrated that this drug is a powerful stimulant of the pancreatic secretion. Ch. Dubois found that 1 gm. of chloral injected into the duodenum or jejunum exerted a powerful influence on the secretion of bile. This observer states that its action was very much weaker when it was injected into the rectum or into the blood vessels, and an amount (25 cgms.) which no longer had any excitatory effect when injected into these organs still caused a flow of bile when injected into the duodenum. According to Fleig, about 15 minutes elapse after the injection of chloral into the blood stream before any acceleration in the secretion of bile occurs, while after intraduodenal injection it takes place almost immediately. He also observed that the injection of chloral into the duodenum still further augmented the increase in secretion produced by a previous intravenous injection, but that no augmentation occurs after injection into the ileum or rectum. The effect of the intravenous injection of an extract of duodeno jejunal mucous membrane treated with chloral is comparable in its effect on the secretion of bile to that of the injection of chloral into the duodenum. From these results Fleig concluded that the mechanism by which the secretion of bile occurred after introduction of chloral into the duodenum was chiefly humoral, though from experiments in which he used the method previously quoted in this paper, reflex action also appeared to play some part. The following experiments confirm the fact that chloral introduced into the stomach has a very strong excitatory effect.

TABLE LII. *Dog C.* Effect of 1 gm. of chloral hydrate in 50 c.c. of water. 24. 3. 15.

	Bile c.c.	Solids gms. in 1 c.c.
1st hour (fasting)	4·1	·082
2nd „ „	3·8	·083
1st hour after administration	7·2	·064
2nd „ „ „	8·3	·042
3rd „ „ „	7·7	·041
4th „ „ „	6·0	·044

TABLE LIII. *Dog E.* 1 gm. chloral hydrate in 100 c.c. of water. 11. 6. 15.

1st hour (fasting)	3·9	·076
2nd „ „	3·2	·078
1st hour after administration	6·4	·045
2nd „ „ „	8·0	·041
3rd „ „ „	9·7	·042
4th „ „ „	6·4	·042

10. *The effect of some hepatic poisons.*

(*a*) *Atropine.* The well-known effect of atropine on the secretion of such glands as the salivary, gastric and pancreatic, has suggested the investigation of its action on the secretion of bile. Rutherford, Vignal and Doods found that atropine caused no diminution in the flow of bile but that it antagonised the effect of physostigmine on the liver, while Prévost and Binet on the other hand state that it does inhibit the biliary secretion. In my experiments a slight diminution resulted shortly after the injection.

TABLE LIV. *Dog C.* 4. 2. 15.

	Bile c.c. in 15 mins.		Solids gms. in 1 c.c.
1 (fasting)	1·9		
2 „	1·7		·059
Hypodermic injection of 1 c.c. normal saline solution.			
1	1·9		
2	2·1		
3	2·0	7·9	·048
4	1·9		
Hypodermic injection of 0·01 gm. atropine sulphates.			
1	0·9	Pupils extremely dilated	
2	1·4		
3	1·7	5·8	·052
4	1·8		

Owing to the excitement of the dog, the experiment was discontinued.

TABLE LV. *Dog B.* Fed with 300 gms. of meat about 18 hours before the experiment. 18. 2. 15.

	Bile c.c. in 15 mins.		Solids gms. in 1 c.c.
1 (fasting)	1·8		
2 „	1·7	7·2	·042
3 „	1·9		
4 „	1·8		
Hypodermic injection of 0·003 gm. sulph. atropine.			
1	0·8		
2	*0·3	4·3	·037
3	1·8		
4	1·4		
5	1·2		
6	1·1	4·6	·031
7	1·0		
8	1·3		
9	1·5		
10	1·0	4·4	·031
11	1·3		
12	0·5		

* Pupils extremely dilated.

(*b*) *Pilocarpine.* This drug, though a powerful excitant of the salivary secretion, has only a slight influence on the secretion of gastric juice and, according to many authors, no influence on the secretion of bile. My experiments however show a slight increase in the flow of bile as a result of the hypodermic injection of pilocarpine.

TABLE LVI. *Dog C.* 15. 3. 15.

	Bile c.c.	
1st hour (fasting)	2·0	
2nd „ „	2·6	
Hypodermic injection of 0·005 gm. pilocarpine hydrochlorate.		
1st hour	3·1	Salivation and vomiting
2nd „	3·4	of slime.
3rd „	3·2	

TABLE LVII. *Dog E.* 22. 6. 15.

	Bile c.c.	Solids gms. in 1 c.c.	
1st hour (fasting)	4·9	·054	
2nd „ „	4·3	·052	
Hypodermic injection of 0·002 gm. pilocarpine hydrochlorate.			
1st hour	6·4	·035	(salivation)
2nd „	5·2	·034	
3rd „	5·0	·032	

(*c*) *Nicotine.* It has been found by Babkin(28) that the effect of the injection of nicotine is more marked in the case of the gastric secretion than in that of the salivary secretion and that the secretion does not begin until from 45 to 80 minutes after the injection. In one experiment, as a result of the injection of 0·02 gm. nicotine, he obtained 62 c.c. gastric juice, 12 c.c. saliva, and 32 c.c. bile. I found that this drug was in some cases effective in causing an increase in the secretion.

TABLE LVIII. *Dog C.* 17. 3. 15.

	Bile c.c.	
1st hour (fasting)	3·5	
2nd „ „	3·2	
Hypodermic injection of 0·01 gm. nicotine sulph.		
1st hour	3·2	Vomiting of slime (neutral reaction)
2nd „	4·3	
3rd „	4·1	

TABLE LIX. *Dog E.* 24. 6. 15.

	Bile c.c.	Solids gms. in 1 c.c.	
1st hour (fasting)	4·4	·058	
2nd „ „	4·1	·057	
Hypodermic injection of 0·004 gm. nicotine sulph.			
1st hour	5·3	·033	Vomiting of slime
2nd „	8·0	·031	
3rd „	6·7	·032	

(*d*) *Alcohol.* Prévost and Binet, Albertoni and Barbéra found that alcohol had no excitatory effect on the elimination of bile. I found however that the results varied after the administration of alcohol and that large doses produced an increase.

TABLE LX. *Dog C.* Introduction of 100 c.c. 10 % alcohol. 12. 3. 15.

	Bile c.c.
1st hour (fasting)	2·2
2nd „ „	2·8
1st hour after introduction	2·9
2nd „ „ „	2·8
3rd „ „ „	2·6

TABLE LXI. *Dog E.* Introduction of 200 c.c. 10 % alcohol. 28. 6. 15.

1st hour (fasting)	4·1
2nd „ „	5·0
1st hour after introduction	6·3
2nd „ „ „	6·0
3rd „ „ „	5·2

TABLE LXII. *Dog E.* Same conditions as the above. 30. 6. 15.

	Bile c.c.
1st hour (fasting)	5·3
2nd „ „	5·6
1st hour after introduction	7·6
2nd „ „ „	6·4
3rd „ „ „	5·7

SUMMARY OF CONCLUSIONS.

1. There is little difference in the effects on the secretion of bile during the first six or seven hours between the diets of bread, butter and meat, if these substances be administered in quantities of corresponding caloric value. In the case of bread the diminution in secretion occurs sooner than in the case of butter or meat.

2. Starvation tends to diminish the secretion of bile and the excitatory effect of feeding on the liver cells.

3. The following substances introduced into the stomach cause an increased secretion of bile:

Raw white of egg (if digestion occurs).
Boiled egg white.
Fat and oil.
Soap solution.
Acids (very marked).
Witte's Peptone.
Liebig's extract of meat.
Bile-salts, or bile.

All these substances produce an increased secretion of a more dilute bile, with the exception of bile and bile-salts, which produce a bile lighter in colour but with a larger percentage of solids.

4. Secretin injected into the blood stream causes increased secretion of a more dilute bile.

Intravenous injection of Witte's peptone has a similar effect.

Injection of hæmoglobin solution into the blood stream increases the pigments of the bile without marked change in the amount.

5. The following substances eaten or introduced into the stomach produce little or no effect.

Pure cane sugar.
Cakes of baked starch and sugar.
Water.
Solution of sodium bicarbonate.

6. The following drugs increase the flow of bile:
   Sodium salicylate (markedly).
   Salol (slightly).
   Chloral hydrate (markedly).
   Cream of Tartar.
   Alcohol (in large doses).
   Calomel is without effect.

7. Atropine causes a slight diminution, pilocarpine a slight increase, and nicotine gives an inconstant increase of secretion.

The subject of this paper was suggested by Prof. E. H. Starling, to whom I am indebted for performing the operations, and also for advice and criticism throughout the research.

REFERENCES.

(1) Nasse and Ritter. Quoted from Stadelmann. Der Icterus. 1897.
(2) Bidder and Schmidt. Quoted from Hermann's Hdb. d. Physiol. v. S. 256.
(3) Prévost and Binet. Revue méd. de la Suisse rom. p. 249. 1888.
(4) Rosenberg. Arch. f. Physiol. XLVI. S. 334. 1890.
(5) Barbéra. Arch. ital. de Biol. XXIII. p. 165. 1895.
(6) Doyon and Dufourt. Arch. de Physiol. p. 562. 1897.
(7) Fleig. Arch. internat. de Physiol. p. 286. 1904.
(8) Rutherford, Vignal and Doods. Trans. Roy. Soc. Edin. XXIX. p. 133. 1880.
(9) Wertheimer. Compt. rend. Soc. de Biol. LV. p. 286. 1903.
(10) Bayliss and Starling. This Journal, XXVIII. p. 325. 1902.
(11) Brüno and Klodnizki. Quoted from Babkin, Die äussere Sekretion der Verdauungsdrüsen. S. 344.
(12) Walter. Quoted from Babkin. Ibid. S. 344.
(13) Bernard. Leçons de physiol. expér. p. 429. 1856.
(14) Küthe. Stud. d. physiol. Instit. zu Amsterdam. 1861.
(15) Wertheimer. Journ. de Physiol. et de Path. gén. p. 1061. 1902.
(16) Matsuo. This Journal, XLV. p. 447. 1912–13.
(17) Asher and Barbéra. Quoted by Fleig, Arch. internat. de Physiol. p. 286. 1904.
(18) Schiff. Arch. f. Physiol. III. S. 598. 1870.
(19) Socoloff. Arch. f. Physiol. XI. S. 166. 1875.
(20) Tarchanoff. Arch. f. Physiol. IX. S. 53 1874.
(21) Vossius. Quoted from Stadelmann. Der Icterus. 1897.
(22) Stadelmann. Der Icterus. 1897.
(23) Pfaff and Balch. Quoted from Petrowa, Journ. of Exper. Med. II. 1897.
(24) Petrowa. Ztsch. f. physiol. Chem. LXXIV. S. 429. 1911.
(25) Gottlieb. Arch. f. exper. Path. u. Pharm. XXXIII. S. 261. 1894.
(26) Wertheimer and Lepage. Compt. rend. Soc. de Biol. LII. p. 668. 1900.
(27) Dubois. Quoted by Wertheimer (9).
(28) Babkin. Die äussere Sekretion der Verdauungsdrüsen. 1914.