OBSERVATIONS ON THE SECRETION AND COMPOSITION OF HUMAN BILE

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(Received March 16th, 1912)

An opportunity having offered for making some observations on the secretion of bile in the human subject in a case of biliary fistula, it has appeared advisable to record the results obtained, though it is recognised that in themselves these observations do not lead to any definite conclusions, and are only of value as confirming, or otherwise, accepted teaching or as offering suggestions for further work.

The patient was a woman, aged 24, who had been operated on in October, 1911, for acute suppurative cholecystitis with gall-stones. The gall-stones and half of the gall bladder were removed. The wound was drained for a time, but had healed five weeks after the operation. It remained healed for two days, then broke down with the formation of a fistula. Jaundice was present before the operation, but after operation, in the opinion of the surgeons, the common bile duct was not completely blocked. The faeces were said to be light coloured. Apart from the fistula the woman's health was good.

The research was undertaken on Professor Bainbridge's suggestion, the primary object being to ascertain the immediate effect, if any, on bile secretion of the administration of protein, carbohydrate, fat or hydrochloric acid. It was, of course, impracticable to introduce these substances into an absolutely empty stomach, and therefore pure results could not be anticipated. Moreover, inasmuch as the common bile duct was presumably patent, though probably constricted, the further difficulty had to be allowed for that the results obtained by the collection of the fistula bile would be unreliable in so far as there was a passage of an unknown quantity of the secretion into the intestine. With a view to minimising this source of error, arrangements were made for the examination of the faeces, but unfortunately owing to a series of misunderstandings the stools were never obtained. The pale colour of the faeces and the probability that the common bile duct was thickened as a result of the original disease make it reasonable to suppose that only a small quantity of bile, if any, found its

way into the intestine. Making full allowance for these difficulties, there are still some points of interest to be found in the results obtained.

The bile was collected by a tube similar to that employed for bladder drainage after suprapubic cystotomy. It was measured at intervals of five, ten or fifteen minutes, but it was found that the results were most instructive if the fifteen-minute interval was adopted throughout, and accordingly in the subjoined charts each second ordinate represents a fifteen-minute interval. The patient was in bed throughout the whole period of observation. The charts show the rate of flow in relation to the diet, each abscissa representing 0·5 cubic centimetre of bile and every second ordinate a quarter-hour period. With each is given the total quantity collected and a note of the nature of the pigment.

FIG. I. Bile in 11 hours 239 c.c. (8 p.m. to 8 a.m., 22nd, 99 c.c.) Colour, brown. Night bile darker in tint than day bile. In this and the succeeding charts, the abscissae represent 0·5 c.c., and each second ordinate indicates a 15 minute period.

Fig. I shows the rate of flow during one day on ordinary hospital diet. The curve divides itself into three periods, the first of three and a half hours from 9-30 to 1 o'clock, ending in a sharp fall within half an hour after the midday meal; the second of three hours from 1 to 4, ending in a sharp fall immediately after tea; and the third of four hours from 4 to 8, showing a slight fall after supper at 6 o'clock and a final fall at the end of the curve. The average flow for each quarter-hour during the first

period was 8.3 c.c., during the second period 6.5 c.c., and during the third 2.3 c.c. The flow from 8 p.m. to 8 a.m. the next day totalled 99 c.c., or an average for each fifteen minutes of 2 c.c. There are thus two main features of interest in this curve, (1) the progressive fall in the output from morning till evening, and (2) the sudden diminution after the midday and afternoon meals. The suddenness of the fall within at most half an hour of the meal suggests four possibilities, (1) a mechanical interference with the flow by pressure of the distended stomach on the portal fissure, (2) inhibition of the secretion, (3) diversion of the flow to the common bile duct, or (4) removal of a normal stimulus. Mechanical interference is *a priori* improbable, and is made more so by the fact that there was no increase in the flow from the fistula as the stomach contents diminished, but, on the contrary, the rate of flow remained at the lower level. Inhibition either by chemical or nervous means would be contrary to the known facts with regard to other secretions in connection with the digestive system. With regard to the possibility of a diversion of the flow into the duodenum, it is common knowledge that no flow of bile into the intestine occurs normally so soon after food is taken, and the question remains whether this fall has any association with the previous meal. Normally, of course, the gall bladder empties itself a few hours after a meal is taken, and it may be assumed that the contraction of the gall bladder is accompanied by some degree of dilatation of the bile duct. Mr. R. J. Willan informs me that in a case of duodenal fistula in the Royal Victoria Infirmary, Newcastle, a gush of partially digested food mixed with bile escaped with great regularity from three to four hours after each meal. If this is the normal time for the outflow of bile in the human subject, it is obvious that the diminished flow in this case coincides with the normal period for escape of bile into the duodenum in relation to the previous meal, and the occurrence immediately after food may be a pure coincidence. On the other hand, the meal at 9 a.m. was a very light one, consisting of soup; and again on the 22nd November, when the midday meal was given an hour earlier than usual, the diminution of flow also occurred earlier. Professor Bainbridge has suggested the fourth possible explanation which appears to be the most probable, viz., that as a result of the entrance of the meal into the stomach the pyloric orifice is closed for a time, and the normal stimulant for the production of secretion is thus withdrawn, leading to a diminished flow until digestion has proceeded for a time and chyme again begins to pass into the duodenum.

I had no opportunity of repeating this full-day collection, but it is

noteworthy that the quantity of bile collected during the midday hours in the subsequent experiments, with two exceptions to be discussed later, agreed closely with the quantity during the same hours on the normal day. The quantities obtained between the hours of 11 a.m. and 1 p.m. on the seven days were as follows (11.10 to 1.10 on the 28th):—

21st	...	...	...	81 c.c.
22nd	...	...	...	59 c.c.
23rd	...	...	...	18 c.c.
24th	...	...	...	77 c.c.
25th	...	...	...	85 c.c.
26th	...	...	...	75 c.c.
28th	...	...	...	84 c.c.

On the 22nd a solid meal was taken an hour before the usual time, between 11 and 12 instead of between 12 and 1, and the corresponding fall in the rate of flow took place before 1 o'clock. The small quantity obtained on the 23rd will be discussed in relation to the diet. Omitting these abnormal days, it will be seen that the rate of flow at this period of the day is remarkably constant, and gives some support to the possibility that Fig. I represents a normal rate of secretion.

As will be seen from Fig. II, a carbohydrate meal with a negligible amount of protein was given on November 22nd instead of the customary midday meal, and about an hour before the usual time for that meal. It was followed by a diminution in the rate of flow similar to that observed in connection with the ordinary meals on the 22nd, but the curve shows a sharp rise followed by an equally sharp fall two hours after the meal. This rise appears to be due to a sudden gush, possibly from some mechanical cause such as a change of position, and the average rate of flow for two and a quarter hours after food is just under 7 c.c. per quarter-hour.

The absence of protein in this day's food appears to be the only explanation available for two peculiarities which appeared on the following days. On November 23rd the flow was markedly diminished (Fig. III), only 28 c.c. being obtained in six hours, or an average of just over 1 c.c. per quarter-hour. This came mainly in three gushes, two of which followed the administration of cream and soda, but, in the light of the other experiments, were probably independent of this. The third gush occurred just before tea without any perceptible cause.

The second peculiarity which may possibly be due to the carbohydrate diet was that on November 24th, the second day after the non-protein food,

the bile was markedly green in colour. This green colour persisted for three days, till on the night of the 26th the bile showed a preponderance of brown, and on the 28th (no bile was collected on the 27th) the colour was again the normal brown of human bile. Kunkel¹ states that in dogs the sulphur taken in protein is excreted partly in the bile, and that whereas the excretion of protein sulphur in the urine takes place on the same day on which the protein food is taken, the increase in the biliary sulphur does

FIG. II. Bile in 2½ hours 81 c.c.
Colour, brown.

FIG. III. Bile in 6 hours 28 c.c.
Colour, brown.

not appear till two or three days later. In view of that fact, it appears possible that the green colour of the bile, appearing in this case from the second to the fourth day after that on which the carbohydrate food was taken, may be traceable to the nature of the food. This is especially possible when one remembers that the bile of herbivorous animals is habitually green in colour.

Hydrochloric acid (half a pint of 0.2 per cent. solution) was administered with a view to stimulating the production of secretin. As Hertz² has shown that food begins to leave the stomach very shortly after a meal, and as the present observations appear to indicate that no marked constriction

1. Quoted by Noel Paton in Schäfer's *Physiology*.
2. *Brit. Med. Journal*, 1912.

of the pylorus follows the ingestion of fluid, it may be assumed that any increase in the flow of bile will be due to the influence of the acid in stimulating the production of secretin, the fact that secretin does excite the flow of bile having been demonstrated by Bayliss and Starling.¹ The chart shows that such an increase did occur (Fig. IV). The flow averaged over 12 c.c. per fifteen minutes during two and a half hours after the administration of the acid, in spite of the fact that some bile was lost by leakage. A repetition of the experiment on November 28th confirmed this result (Fig. VII), the fifteen-minute average during one and three-quarter hours after the acid was given being 11.4 c.c.

FIG. IV. Bile in 3½ hours 129 c.c.
Colour, markedly green

FIG. V. Bile in 2½ hours 98 c.c.
Colour, distinctly green.

Peptone (Fig. V) and bovril (Fig. VI) did not appear to have any marked immediate effect on the flow of bile, the average flow for fifteen minutes during one and three-quarters hours after the administration being 10 c.c. and 9 c.c. respectively, or about the average rate for the period of the day at which these substances were given. It is worthy of note, however, that the amount collected on the 26th and during the night of the 26-27th was above the average (see below), and the question arises whether this increase

1. *Journal of Physiology*, Vol. XXVIII, 1902,

is in any way connected with the increased nitrogenous intake. The peptone was administered on the 25th and the bovril on the 26th, in each case during the forenoon and in addition to the ordinary meals. The increased flow occurring on the day after the addition of the peptone to the diet is in sharp contrast to the great diminution which occurred on the day after a protein-free diet, and supports the suggestion that the remote metabolism of protein food is a factor in bile production.

FIG. VI. Bile in 3 hours 114 c.c. (8 p.m. to 8 a.m., 27th, 266 c.c.) Colour—in day bile, green preponderates; in night bile, brown.

FIG. VII. Bile in 2½ hours 110 c.c. Colour, brown.

TOTAL DAILY QUANTITY

The total quantity obtained on the 21st-22nd in twenty-three hours was 338 c.c., and the quantity for twenty-four hours may therefore be estimated as 350 c.c. This was on ordinary diet. On the 26th-27th 380 c.c. were collected in fifteen hours, giving an estimated total for twenty-four hours of about 600 c.c. This was, as stated above, after an increased nitrogenous intake during the previous two days. Previous observations¹ of the daily quantity of bile secreted in the human subject

1. Quoted in Gamgee's *Physiological Chemistry of the Animal Body*, Vol. II, 1893,

show results varying from 374 c.c. (Yeo and Herroun) to 850 c.c. (Mayo Robson). Ranke obtained 636 c.c., von Wittich 542 c.c., Copeman and Winston 779 c.c., and Paton and Balfour 590 c.c. These figures would indicate that in the case under investigation a very considerable proportion of the daily secretion was obtained through the fistula.

COMPOSITION

Several analyses were made, the charcoal method being chiefly used, but these only confirmed the accepted figures for fistula bile. It was found that the bile secreted by night had virtually the same composition as that obtained during the day. As a rule the night bile had a slightly higher specific gravity, approximating to 1,011 when the day bile was 1,010, and the night bile of the 21st-22nd was distinctly darker in colour than the day bile. The results of analysis were almost identical with those of Jacobsen¹, who found the solids in his case (also fistula bile) amounted to 2·26 per cent. In the present case 9·275 grams of day bile (November 26th) yielded 0·209 gram or 2·253 per cent. of solids. 10·074 grams of the corresponding night bile yielded 0·217 gram or 2·253 per cent. of solids. The ash of the day bile equalled 0·582 per cent. of the total bile, and that of the night bile 0·516 per cent. But whereas Jacobsen found over 1 per cent. of glycocholate of sodium, I found the bile salts always under 0·5 per cent. A typical result is the analysis of the night bile of November 26th-27th:—

Water	...	...	97·747
Total solids	...	...	2·253
Bile Salts	...	...	0·416
Cholesterol	...	...	0·094
Lipoids	...	...	0·298
Ash	...	...	0·516

This leaves 0·929 for mucin and pigments.

REMARKS

The observations recorded in this paper are much diminished in value by the uncertainty as to the condition of the common bile duct and the absence of information as to the quantity of bile which may have found its way into the intestine. They indicate, however, that the composition

1. Quoted in Gamgee's *Physiological Chemistry of the Animal Body*, Vol. II, 1893.

of day and night bile is the same, and they suggest that the effect of food substances on bile secretion may show themselves from the second to the fourth day after ingestion, in agreement with Kunkel's results¹ on sulphur excretion. They further appear to support Starling's statement² that 'As an excretion the production of bile must be continuous, and related, not to the processes of digestion, but to the intensity of the destruction of the red corpuscles.' They raise the question as to whether the more remote metabolism of the ingested food may not have an equal share with the destruction of red corpuscles in determining the amount of secretion, thus throwing doubt on what Moore³ has said, that 'No connection exists between the amount of proteid metabolism and the amount of cholates produced, such as would be found if the cholates were a channel for the excretion of the nitrogen and sulphur of proteid decomposition products.' They accord rather with Spiro's statement⁴ that nitrogen and sulphur are increased in bile by a protein diet, and with that of Rosenberg and Barbera⁵ that in dogs both bile and its solid constituents are increased after protein food.

I have to express my thanks to Professor Rutherford Morison for permission to make these observations on his patient. I am very greatly indebted to Professor Bainbridge who initiated the work and has helped me throughout with his advice. I would also especially thank Mr. R. J. Willan for arranging for the special diet and for organising the collection of the bile and applying the collecting apparatus. Finally, I am indebted to the nurses and dressers who willingly undertook the task of keeping the necessary log.

1. *Loc. cit.*

2. *Recent Advances in the Physiology of Digestion*, 1906.

3. Schäfer's *Physiology*, Vol. I.

4 and 5. Quoted in Schäfer's *Physiology*, Vol. I, by Noel Paton.