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ELLIOTT P. JOSLIN

(From the laboratories of the Harvard Medical School and the
Massachusetts General Hospital, under the direction
of Dr. FRANZ PFAFF)

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INFLUENCE OF BILE ON METABOLISM.

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(From the laboratories of the Harvard Medical School and the Massachusetts General Hospital, under the direction of Dr. Franz Pfaff.)

The incentive to this work came from my friend and instructor Dr. Franz Pfaff, to whose unvarying interest, suggestions, and encouragement it is chiefly due. In an article by Dr. Pfaff and Alfred W. Balch¹ on "An Experimental Investigation of Some of the Conditions Influencing the Secretion and Composition of Human Bile," it was shown that human bile, oxbile, and bile salts when given to a patient with complete biliary fistula had a marked cholagogic action. The experiment extended over a period of ninety-seven days, and represents the most complete study of the question on a human being yet produced.

During this investigation it was observed that while the patient was taking bile in one form or another the appetite improved, the bowels moved without medication, and the stools diminished in bulk, but increased in consistency and color.

The above article closes with the following paragraph: "For the present we will only say that bile may be useful in those cases where so-called cholagogues are now prescribed as well as in certain cases of constipation, and possibly cases where we wish to increase the absorption of fat."

The influence of bile on metabolism has been chiefly studied in a negative way by observing the changes which have occurred when bile was removed from the intestinal tract by means of a biliary fistula. In the present instance the effect of bile has been shown in a positive manner by the direct administration of the same under similar conditions.

¹ The Journal of Experimental Medicine, Vol. II., No. 1, 1897.

A preliminary report of a portion of the work done under the provisions of the second Dalton Scholarship at the Massachusetts General Hospital for the years 1898-1899.

The present study was made upon¹ a woman of fifty-four years of age who had suffered from attacks of gall-stones covering a period of three years. She was operated upon in the hospital, but her condition was so critical that the gall bladder alone was emptied of stones. She rallied quickly from the operation. The stools were colorless, and chemical tests failed to show the presence of bile acids. As it seemed best for her to remain in the hospital for some time to gain strength, the opportunity was afforded for special study of the case, which was carried on between December 20 and December 31, inclusive.

During the preceding fourteen months the action of bile on the metabolism of a healthy individual had been investigated and the same question studied on four dogs, upon whom the common duct was ligated and cut and a biliary fistula then made. The results thus obtained, together with the complete account of this case, will be reported later.

This experiment was divided into three similar periods of four days each, except that in the second period the patient received thirty grams of dried oxbile. The beginning and end of the experiment and the different periods were all marked off by the patient's taking the charcoal mixture recommended by Müller. In each instance the change in the period was definite. During the twelve days the patient passed about two-thirds of the twenty-four hours in bed, and for the remainder of the day was about the ward. The bowels showed no tendency at any time to constipation or diarrhœa.

During this time the diet of the patient consisted essentially of bread and butter, thin cream, eggs, sugar, and beef. The per cent. of nitrogen and fat was determined in each article of food, daily double analyses being made in the case of the thin cream. All the food was prepared in the laboratory by Mrs. Lillian Osborne, the assistant in the chemical laboratory of the Massachusetts General Hospital.

The urine was collected daily and the amount and specific

¹ The patient was in the services of Dr. H. H. A. Beach and Dr. Maurice H. Richardson at the Massachusetts General Hospital, and the operation was performed by Dr. S. J. Mixer. To all these gentlemen I am especially indebted for the privilege of conducting these investigations.

gravity noted. The nitrogen in two portions of 5 cc. from the twenty-four hours' amount was determined by the Kjeldahl method, and the urea with Squibb's apparatus. The stools for each period, with the wash-water made use of in cleaning the utensils, were made slightly acid with a few drops of concentrated sulphuric acid, and were then evaporated over the water-bath, especial care being taken that they be thoroughly and frequently stirred. The stools did not become solid while over the water-bath, but on removal from the same assumed a firm consistency, though not sufficiently so to allow of reduction to a powder. They were then weighed and the total per cent. of fat determined by double analyses.

The bile was collected at six-hour intervals and the amount, specific gravity, and the per cent. of solids in the twenty-four hours' amount determined. The fistula caused much annoyance, as it did not admit of the satisfactory use of a Pegram's cannula. Dr. LeCompte tried many other devices, but it was impossible to prevent leakage. On this account the bile, not collected in the flask the patient wore, was caught in the dressings which were arranged for this purpose. The bile was then removed from them by repeated soakings in water, which was later siphoned off, filtered, and the filtrate evaporated to constant weight, which weight was that of the dried bile. As the per cent. of solids in the bile each day had been calculated, the amount of bile absorbed in the dressings was easily estimated. That the method was sufficiently accurate is shown by a comparison of the amount of bile in the first and third periods (which is seen to be nearly the same), because in the first period there was no leakage from the cannula, while in the third but a half was secured in this way, the remainder being caught in the dressings.

Bile was given to the patient in the second period in the form of bile pills. Each pill represented 0.25 grams dried oxbile. To render these more palatable and less liable to change in the stomach they were coated with salol—59 grains to the 100 pills. Of these the patient took 30 daily, a total of 120 in 4 days, or 30 grams oxbile and 4 grams salol.

Following the above plan, the results which are summarized below were obtained:

1. The amount of urine increased over 50 per cent. in the bile period. V. Noorden has recorded a similar increase in the amount of urine following the removal of the obstruction in acute catarrhal jaundice. But so far as I am aware the diuretic effect of bile *per se* has not as yet been proven. That the salol coating, which amounted to about 1 gram a day, is not sufficient to account for this diuretic action of the bile pills is evident from the work of Kumagawa who gave 2 grams sodium salicylate daily to a dog of 25 kilos, without essentially changing the amount of urine secreted. Though various authors speak of the diuretic action of salol, none have refuted Kumagawa's experiments, and none have claimed for it an action equivalent to that recorded in this experiment.

2. The per cent. of fat lost in the stools in our patient was 63 per cent., which closely corresponds to the results Müller obtained in human beings and dogs with complete obstruction of the common duct. Under bile medication the stools contained 23 per cent. less fat than in the first period, and 17 per cent. less than in the third. This represents an actual diminution of the amount of fat lost in the stools. Looking at it from another standpoint, the average digestion of fat in the periods without bile was 40 per cent.; when bile was given with the food this figure rose to 60 per cent., — *i.e.*, bile increased the digestion of fat relatively by 50 per cent.

3. Thirdly, there was a marked improvement in the assimilation of nitrogen by the body. Instead of an average of 15 per cent. being lost in the faeces, but 7 per cent. escaped digestion during the four days the patient took bile. The reason for this, perhaps, lies in the better digestion of fat at this time, and the better exposure thereby of the proteid elements of the food to the digestive juices.

4. The amount of bile solids secreted in the bile period was 47 per cent. greater than in the periods coming before and after, and thus affords confirmation to the work of Pfaff and Balch here in Boston on a human being, and that of Stadelmann and his pupils in Germany on dogs.

5. Your attention is called to the statement in the article above cited that no constipation was experienced by the patient while she took bile. Though the bowels moved daily throughout the whole of our experiment the patient tells me that when taking bile pills they always moved more satisfactorily. It is by no means every case of sluggish bowels which finds stimulation in bile pills, and at present I know of no way of determining cases suited to their action save by empirical means.

6. As to the general effect of bile on body metabolism, it was observed that the urea and nitrogen were secreted in greater amount in the bile period than in either of the others. No definite conclusions can be drawn from this fact, because more nitrogen was ingested during these four days; and even apart from this it must be borne in mind that in this regard salol alone can play an important rôle.

Since the conclusion of this experiment the patient has been operated upon again. The common duct was found occluded with gall-stones of soft consistency. These were removed by an incision in the duct, and its complete patency into the duodenum once more established. The fistula has ceased to discharge and the patient is now well. This happy outcome led Mrs. Mc. to undergo another metabolism experiment of three days' duration for the purpose of comparing her digestion in health with that when no bile was able to enter the intestine, and the results will be briefly stated.

1. The volume of urine was 815 cc. per day, which is about the amount of the second period of the first experiment in which the patient was artificially supplied with bile and double that of the other periods. This lends weight to the conclusion already reached that bile is a diuretic.

2. The amount of fat lost in the stools was about 15 per cent. of that ingested.

