jected. Thus in a guinea-pig which received subcutaneously a quarter of a cubic centimetre of virulent peritoneal fluid there was a swelling at the site of inoculation, which ended in a slowly forming abscess pointing in 11 days; a pure culture of the bacillus was obtained from it. The animal was killed on the twelfth day and a pure culture of the bacillus was obtained from the abscess, but the heart's blood, the spleen, the liver and peritoneum were sterile; the heart muscle was not degenerated. Chantemesse and Widal and others have, however, found that infection of the body can occur after subcutaneous injection of the bacillus, and this occurs readily if the process of infection be aided in the manner previously described.

It is interesting to note in this series of experiments the absence of leucocytes in the peritoneal exudation as the bacillus became more virulent; and the formation of an abscess and the limitation of the growth of the bacillus when the virulent virus was injected under the skin.

TOXIC ACTION OF THE PERITONEAL FLUID.

It has been stated that the cause of death when the virulent peritoneal fluid is injected into a rabbit or a guinea-pig was due more to the action of a chemical poison than to the growth of the bacillus, since this occurred so rapidly; in one case in five and a-half hours, and following intravenous injection in two and a-half hours.

The effects of this chemical poison were examined by filtering the peritoneal fluid through porcelain, in a small apparatus improvised for the purpose. In the first experiment $\frac{1}{2}$ c.cm. of this filtered sterile peritoneal fluid was injected into the marginal vein of a young rabbit. A moderate degree of fever followed the injection for several hours. Subsequently the temperature fell to the normal, and no symptoms were observed in the animal, which died at the end of thirty days. The heart's blood was sterile, and the heart muscle showed well-marked degeneration of the fibres—there being loss of striation with longitudinal fibrillation, and the presence of numerous small granules staining black with osmic acid. Other experiments were done in a similar manner, using 1 c.cm., 1.5 c.cm., and 2 c.cm. of the filtered peritoneal fluid. In all cases some degree of fever followed the injection, but no effect was subsequently observed, and death did not occur. The filtered peritoneal fluid was therefore not nearly so poisonous as the unfiltered; evidently the porcelain filtrate had kept back the greater part of the chemical poison, whether this was present in the albuminous fluid or in the bodies of the bacilli.

EXAMINATION OF THE POISON IN THE FRESH STATE IN THE SPLEEN.

Before continuing this part of the subject, we must return to the consideration of the poisons present in the spleen of typhoid patients. In all the cases examined, as has been stated, the typhoid bacillus was present in large quantities, and in only one was there an admixture with another bacterium, the bacillus coli.

The splenic pulp was rubbed through sterile wire gauze and treated with about 500 c.cm. of sterile normal salt solution. This was allowed to stand a short time, and an attempt was made to filter it through porcelain. This was a matter of great difficulty, only a small amount of the liquid passing through. It was thin and deeply blood-stained. It was injected into the marginal vein of a rabbit on two consecutive days—4 c.cm. on the first day and 3.5 c.cm. on the second day. No appreciable effect on either the temperature or the body weight followed the injection on either day or on the subsequent two days; but on the fifth day of the experiment the temperature was found to have fallen to 97.6°, and the animal was collapsed and had profuse and mucoid diarrhoea. The temperature remained subnormal the whole of that day, and at 10 o'clock on the sixth day it was 95.4°, and the animal was lying motionless on its side, but breathing regularly. It was killed with chloroform. At the *post-mortem* examination there was subcutaneous hæmorrhage over the lower third of the abdomen, extending down over the upper third of the front of the thighs. In the abdomen there was a soft blood clot, matting together the omentum and the adjacent coils of the intestine. There was no peritonitis. The thoracic organs were normal,

the intestines were empty, except the upper part of the colon and cæcum, which contained soft fæces. There was no enlargement or redness of the Peyer's patches or of any other part of the mucous membrane. From the peritoneal cavity was obtained a growth of the bacillus coli, but the spleen contained no micro-organisms.

What is interesting in this experiment is that, following the injection of the poison, there was a period of incubation, during which no effect on the body temperature or the weight was to be observed, and that a fall of temperature, associated with great bodily prostration and mucoid diarrhoea, supervened somewhat rapidly. This fall of temperature and the collapse and diarrhoea observed are, as will be seen, to be ascribed to the action of the chemical poison of the typhoid bacillus.

A more extensive chemical examination of the spleen was made by means of the precipitation of the extract with alcohol in order to obtain any albumoses that might be present, as well as to separate the alcoholic extract. The method has already been described. The amount of albumoses obtained from each of three spleens was 0.652 g., 0.37 g., and 0.369 g. When dried they formed a fine whitish yellow and very light powder, soluble in water, and giving a brownish solution, which gave a distinct biuret reaction. The alcoholic extract was yellowish in colour, and was separated from the fatty bodies by precipitation with a large excess of ether. It contained a very large quantity of leucin and tyrosin, which separated out in the form of crystals on evaporation. The final alcoholic extract was a yellowish, sticky, resinous-like substance when dried over sulphuric acid.

The injection of the alcoholic extract into the vein of a rabbit did not seem to produce any effect on the temperature, and no appreciable effect on the body weight. In one case 0.112 g. was injected, and the animal appeared as well after the injection as before; it did not die. There was no diarrhoea, nor were there any symptoms to be noted. The injection of the albumoses also had but slight effect on the animal. In one case 0.2785 g. was injected in three doses into a rabbit weighing 790 g.; a dose of 0.352 g. per kilo. of body weight. After the first injection of about 0.4 g. there was no effect on the temperature. After the second injection of about 0.12 g. there was a rise of temperature, the highest being 105° during the day. After the third injection on the following day of the same amount there was only a slight rise of temperature, but on the succeeding days it was again normal. No symptoms were produced in the animal by these injections except a slight rise of temperature. This effect, therefore, is a very different one from that observed after the injection of the saline extract in a fresh spleen. It may have been, of course, that the poison was destroyed by the alcohol during the course of preparation. This, however, is unlikely, inasmuch as the manipulation was very rapid, the products being separated within three days, and the action of the alcohol on the albumoses being less than 18 hours.

THE ACTION OF CERTAIN DRUGS AND MINERAL WATERS ON THE SECRETION AND COMPOSITION OF HUMAN BILE: AN EXPERIMENTAL INVESTIGATION.

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[ABSTRACT.]

THE investigation of cholagogues is one of the most difficult in the whole domain of pharmacology. The importance of the subject is shown by the number of laborious researches undertaken to determine the action of drugs which are supposed to influence the secretion of bile, and its complexity by the contradictory results obtained. As nearly all recent experimental evidence casts doubt on the existence of so-called cholagogues, it occurred to me that the time would be well spent if I could contribute, even in a minor degree, towards a solution of this very difficult problem. While arrangements were being completed for carrying out a series of investigations on dogs by means of Schiff's amphibolic

biliary fistula in the physiological laboratory of St. Thomas's Hospital, I was informed that a patient with a permanent cutaneous biliary fistula had just left the institution. An interview was immediately arranged with this man, who readily consented to place himself at my disposal for experimental purposes.

In mentioning the history of the patient I wish to acknowledge Dr. Payne's kindness in permitting a reference to the notes of the case.

HISTORY OF THE CASE.

The patient, a man, aged 49, was admitted into St. Thomas's Hospital, under the care of Dr. Payne, on July 19th, 1897, and was operated upon by Mr. Anderson on July 29th. At the operation the gall bladder was found tensely distended, and contained clear fluid. The cause of the obstruction in the common bile duct was not ascertained, though a careful search was made. The opinion expressed at the time was that it was probably due to a small impacted gall stone. As the patient ten months later was in a satisfactory state of health this view is probably correct. He was discharged from the hospital on October 20th. During his stay there his stools were always clay-coloured. His weight on admission was 9 st., on his discharge 8 st. 9 lbs.

When he came under my notice on November 7th his health was moderately good. He was anæmic, and troubled more or less with flatulence, but no organic disease could be detected. His appetite was good, and he took a moderate amount of exercise. He lodged close to the hospital, and brought the bile and urine each day to the laboratory. His height was 5 feet 1 inch, and his weight on November 11th, without clothes, 58 kilogrammes (12 st. 2 lbs.). He only varied 2 lbs. while under my observation, and during the latter part of the period he "felt much better and stronger." His bowels were moved naturally once a day after leaving the hospital, but this action was subsequently modified by the drugs taken.

I asked him to take the same amount of food, liquid, and exercise each day, and impressed upon him the necessity for abiding by these rules, as otherwise my results would be vitiated. In addition he took 36 gr. of purified ox bile daily (12 gr. at 10 A.M., and at 2 and 6 P.M.), thus approximating the experimental conditions to the normal standard.

METHOD OF COLLECTING THE BILE.

Arbuthnot Lane's biliary tube was employed, which answered the purpose admirably. By means of sticking plaster, the shield was kept in absolute contact with the skin, so that not a drop of bile was lost. The inner was fastened to the outer tube with a small safety pin to prevent traction. The outer end of the collecting tube was firmly attached to an india-rubber urinary fitted with a stopcock. This allowed the patient to collect the bile at stated times without in any way disturbing the connections. The tube was changed about once a week. During the seventy days the case was under observation, only on two occasions was there any oozing, due to an insufficiency of plaster.

The bile was collected four times a day—at 8 A.M., at 12 noon, at 4 P.M., and at 8 P.M.—and put into different-sized bottles, properly labelled. The specific gravity of each sample was taken at the laboratory temperature, and the same hydrometer was used throughout. Then the four specimens were put into one bottle, shaken, and a portion reserved for analysis.

METHOD OF ANALYSIS.

Bile Solids.—The weight of the capsule was first ascertained, 25 c.cm. of bile measured (the same pipette was always used for this and for estimating the bile salts) and weighed, then evaporated to dryness over a water bath at a temperature of 100° C. The capsule was next placed in a hot-air chamber kept at a temperature of 110° C. by means of a gas-regulating apparatus for at least three hours. After that it was placed in an exsiccator until its weight was constant.

Bile Salts.—To 25 c.cm. of bile about 120 c.cm. of methylated spirit was added, and the whole filtered. The filtrate and washings were evaporated to dryness over a water bath, and extracted with absolute alcohol. The extract was then evaporated to a small volume, and two-thirds of its volume of anhydrous ether added. This was allowed to stand in a cool place for three days, and the precipitate of bile salts was then collected on a weighed filter. The filtrate was again evaporated to dryness, extracted and precipitated as before, and any further precipitate collected on the same filter. The filter was finally dried at 105° C. to constant weight.

I take this opportunity of expressing my gratitude to Dr. Brodie for his advice and for many acts of kindness. I also have to thank Dr. Sikes, Demonstrator of Physiology, for analysing the bile and urine on two occasions during my absence.

CASES RECORDED PREVIOUSLY.

For the purpose of comparing results I will briefly mention the salient facts in the published cases of human biliary fistula.

Monro¹ mentions a case of abscess of the liver where the bile was discharged by coughing, mixed with mucus and saliva. The quantity varied from 10 to 15 ounces in the twenty-four hours. It was irregular in flow, and greater in quantity after dinner.

Charles Robin² mentions a case of Taconi's where a patient had a biliary fistula. The bile amounted to 500 g. in the twenty-four hours.

Harley³ describes a case of hydatids of the liver where the bile was discharged through a fistulous opening, the quantity varying from 16 to 20 ounces.

Murchison⁴ records a case of biliary fistula where the bile flowed at the rate of 1 to 2 ounces per hour, usually increasing after meals.

Frerichs⁵ quotes a case of Roux where 900 g. of bile a day was expectorated.

Ranke⁶ records a case of hydatid disease of the liver where a communication existed between the bile passages and a bronchus. Sometimes the bile was expectorated, while at others it passed into the duodenum. He gives the results of five observations of twenty-four hours' duration when the faces gave no indication of biliary constituents. The patient had chronic bronchitis, and allowance had to be made for the secretion from the respiratory passages. The average of these observations gives 636 c.cm. of bile with 20.6 g. solid.

Noel⁷ mentions a case of biliary fistula. On one occasion 900 g. of bile were secreted in the twenty-four hours, with a specific gravity of 1.009.7.

Von Wittich⁸ has published a case where a biliary fistula formed spontaneously on account of an impacted gallstone. He collected the bile for four hours during the day and for ten hours during the night, and from these data he calculated the amount in the twenty-four hours.

Westphalen⁹ describes a case of liver abscess where the bile found its way into the right pleura, and subsequently after thoracocentesis through the thoracic wall. Taking the average of seventeen days, the bile amounted to 498 g. with 11.266 g. solid. The bile was analysed by Jacobsen. Westphalen tried the effects of water, calomel, and quinine on the biliary secretion. He found that large quantities of water did not increase the secretion nor alter the composition of bile. Calomel and quinine had no effect.

Yeo and Herroun¹⁰ made a number of observations on a case of fistula due to cancer of the common duct. The patient was very ill at the time, and took little nourishment. The average quantity of bile secreted during the twenty-four hours only amounted to 374 c.cm. with 5.044 g. solids. No difference in the rate of secretion was noticed after the small meals taken by the patient.

Hammersten¹¹ records seven cases of biliary fistula, but in all of them a part of the bile found its way into the intestine. The percentage of solids in his cases varied from 1.63 to 3.53 per cent.

Edington¹² published a case of biliary fistula, but the obstruction was incomplete, so that some of the bile escaped into the duodenum.

The next four cases are important, as the patients, apart from the fistula, were in good health at the time of observation, and the obstruction was complete.

Copeman and Winston¹³ record a case of biliary fistula in which the average amount of bile secreted in the twenty-four hours was 770 c.cm., with 11.094 g. solids. They endeavoured to determine the variations in the flow of bile in relation to time and meals.

Mayo Robson¹⁴ reports some interesting observations which he made on a case of biliary fistula. The quantity of bile collected on various dates during the time the patient was in hospital averaged 850 c.cm. Mr. Fairley analysed the bile on two occasions: the mean gives 15.28 g. solids. Mr. Robson investigated the action of the following drugs: Calomel, rhubarb, podophyllin, carbonate of soda, iridin, euonymin, turpentine, and benzoate of soda. Unfortunately, Mr. Robson did not analyse the bile while these experiments were being carried out; he only gives the total quantities collected. He found that iridin increased the flow temporarily, while aerated soda water had the same effect without a subsequent fall. The other drugs had no effect.

Noel Paton and Balfour¹⁵ describe a case of biliary fistula where they made a number of careful observations. They experimented with salicylate of soda, calomel, and ox bile, but at the time the patient was suffering from a moderately high temperature, so that little importance can be attached to their results. They found that salicylate of soda increased both the quantity and the solids, and that although ox bile and calomel influenced the secretion they were less active than the soda salt. A year later, when the patient's health was re-established, Paton¹⁶ had the opportunity of analysing her bile on two successive days. The mean of these observations gave 500 c.cm. of bile with 13.6 g. solids.

The last recorded case is by Pfaff and Balch.¹⁷ Their observations extended over ninety-seven days, and were of a painstaking character. The average of three days without drugs gives 514 c.cm. with 8.57 g. solids. They tried on their patient calomel, corrosive sublimate, salol, ox bile, human bile, and bile salts. Calomel and corrosive sublimate had no effect; if anything, the quantity was diminished, whereas the percentage of solids did not vary from normal. Salol had some influence, but not pronounced enough to justify them in asserting that it was a cholagogue. Human bile, ox bile, and bile salts increased both the quantity and the solids.

THE AMOUNT OF SECRETION IN TWENTY-FOUR HOURS.

In taking the average of the daily amount of bile I excluded those days during which drugs were used, and also the day subsequent to the administration of any drug. Thus the average of sixteen days gave 775 c.cm. of bile: the average of nine days 15.893 g. solids, and the average of six days 4.197 g. bile salts. To save repetition I may state that when the term "without medication" is used it refers to these sixteen days. The specific gravity varied during the period without medication from 1.007.9 to 1.012. A glance at Table I will reveal the fact that the quantity of bile in my case is very similar to that of Copeman's and Winston's, but in mine the total solids are much higher. This I attribute to my patient taking ox bile daily, and also a fair amount of exercise in the open air, while theirs was confined to the wards of a hospital.

TABLE I (modified from Gamgee¹⁸) exhibiting the Results of Different Observers on the Secretion of Bile and Bile Solids (during the Twenty-four Hours) in the Human Subject.

	Ranke.	Von Wittich.	Westphalen.	Yeo and Herroun.	Copeman and Winston.	Mayo Robson.	Paton and Balfour.	Pfaff and Balch.	Bain.
Sex...	M.	F.	M.	M.	F.	F.	F.	F.	M.
Weight in kilogrammes ...	47	—	—	—	43.7	53	73	51	58
Bile secreted in cubic centimetres ...	636	532	498	374	779	849	590	514	775
Bile solids in grammes ...	20.6	—	11.27	5.04	11.09	15.28	13.59	8.57	15.89
Bile secreted per kilo of body...	13.5 c.cm.	—	—	—	17.8 c.cm.	16.0 c.cm.	8.08 c.cm.	10.27 c.cm.	13.36 c.cm.
Bile solids secreted per kilo of body	0.44 g.	—	—	—	0.25 g.	0.18 g.	0.18 g.	0.16 g.	0.27 g.

During the period without medication the smallest quantity of bile was secreted on January 20th—670 c.cm., the largest amount on November 11th—864 c.cm.; similarly, the smallest quantity of solids was secreted on January 24th—15.139 g., whilst the largest was on January 11th—16.640 g.

VARIATIONS IN THE RATE OF SECRETION.

There is abundant proof that the rate of secretion is very irregular, but the conditions which operate to produce this irregularity in flow are, to a certain extent, conjectural. The two most potent factors are probably diet and exercise. It is generally admitted that during digestion the secretion of bile is active, but there is a lack of experimental evidence regarding the kind of diet which most influences the secretion. It appears probable that exercise augments the biliary secretion, but if the exercise produces much perspiration this effect will be annulled. The evidence I have to adduce in support of this statement is exceedingly meagre. On two occasions when the patient was not having drugs circumstances arose which compelled him to take more than his usual exercise. In these two instances the quantity of bile was increased. An average of the days without medication gives the following quantities: From 8 to 12 P.M., 147.7 c.cm.; 12 to 4 P.M., 165.1 c.cm.; 4 to 8 P.M., 148 c.cm.; 8 to 8 A.M., 312.6 c.cm. It will be observed that there is a rise from 12 to 4, which coincides with the principal meal of the day, and the quantity secreted during the day—471 c.cm.—is much larger than that during the night—312 c.cm.

The colour of the bile was always of an olive green, the only variation observed being in depth of tint. The bile was invariably alkaline in reaction.

Dr. Samuel Fenwick¹⁹ has made numerous observations upon the amount of sulphocyanate of potash in the saliva in both health and disease. He noticed a marked decrease in the amount when the activity of the nutritional functions was diminished, and in serious febrile affections he regards an increase as an element of favourable prognostic significance. He expresses his belief that the sulphocyanate salt is derived from the biliary salts after they enter the duodenum, and he bases this opinion on the statement that when the bile is prevented from reaching the alimentary canal, as he says happens in one form of dyspepsia characterised by eructations of sulphuretted hydrogen gas, he found the sulphocyanate salt invariably absent from the saliva. If Dr. Fenwick's hypothesis be correct the salt must be absent from the saliva when the common bile duct is occluded. In order to test this point the patient was asked to discontinue the ox bile pills during the Christmas holidays. His saliva was then examined on several occasions, and the sulphocyanate salt was always present, although the quantity was diminished. His saliva was also examined while he was taking ox bile, but no difference in the reaction could be detected.

THE INFLUENCE OF DRUGS ON THE SECRETION OF BILE.

Before describing my results it would be advantageous to refer very briefly to the experiments performed on dogs in relation to this subject.

Nasse²⁰ was the first to investigate cholagogues. He gave 1 g. of calomel to a dog with a permanent biliary fistula, and came to the con-

clusion that calomel increased the quantity of bile but diminished the bile solids.

Kolliker and Muller²¹ tried calomel and aloes without effect.

Mosler²² and Scott²³ found that calomel did not increase the amount of bile; indeed the latter said it produced a diminution in the quantity and in the solids. These four experimented on dogs with permanent biliary fistulae.

The Committee of which Hughes Bennett²⁴ was chairman, decided that mercuric chloride, calomel, and pil. hydrargyri, did not increase the flow of bile.

Rohrig²⁵ experimented on curarised dogs and rabbits. He counted the drops of bile flowing from the cannula inserted into the open gall bladder, a method open to criticism. Moreover, he gave such large doses (30 drops of croton oil) that his results must be of little value.

Rutherford²⁶ elaborates researches are so well known that a summary is unnecessary. Rutherford asserts that whatever increases the quantity of bile similarly affects the solids, and for that reason he did not consider it necessary to estimate the solids in the greater number of his experiments. I maintain that there are drugs which increase the solids without materially affecting the quantity of the bile, therefore it is incumbent upon the investigator to estimate the solids in all his experiments. Further, I consider the total solids are a more important guide to the influence of a drug on the liver than the quantity of bile secreted. Rutherford attaches great importance to the relationship existing between the quantity of bile secreted and the body weight of the animal. He bases nearly all his conclusions upon this supposed relationship—a relationship, however, which is disproved by referring to Table I. Apart from these criticisms, my results, as far as they go, confirm in the main Rutherford's experiments.

Rosenberg²⁷ used dogs with permanent biliary fistulae. He found salicylate of soda, olive oil, and fats to be cholagogues, the last two being the most powerful. Durand's mixture and Carlsbad salts gave negative results.

Battistini²⁸ found santalin to be the best cholagogue, and in this is corroborated by Marfori.²⁹

Prevost and Binet³⁰ declared that bile itself was the most powerful cholagogue, but turpentine, chlorate of potash, benzoate and salicylate of soda, salol, euonymin, and muscarin were effective. Amongst doubtful substances they placed Carlsbad salts.

Baldi³¹ tried podophyllin, rhubarb, jalap, sodium phosphate, pilocarpin, and Carlsbad water without effect, but ox bile increased the amount and the solids.

Kunkel³² tried large quantities of water, but the quantity of bile was not increased, nor were the solids affected.

Lewaschew³³ found salicylate of soda effectual.

Paschkis³⁴ and Niessen³⁵ obtained negative results with all cholagogues except bile. Since 1890 Stadelmann and his pupils—Niessen, Mandelstamm,³⁶ Müller,³⁷ Loewenton,³⁸ and Glass³⁹ have conducted a series of careful investigations of cholagogues. Stadelmann⁴⁰ summarising the results of these investigations, shows that bile, and possibly salicylate of soda, alone act as cholagogues. He strongly condemns the practice of drawing comparative conclusions regarding the secretion of bile from experiments extending over short periods of time.

Gamgee,⁴¹ commenting on the diversity of these results, suspends his judgment until a fresh research is undertaken on dogs by means of Schiff's amphibolic biliary fistulae. While I agree with him regarding the value of evidence derived from experiments carried out by Schiff's method, it is my belief that fairly reliable results can be obtained in cases of human biliary fistula by the administration of ox bile during the entire investigation. Further, although dogs are more easily controlled than human beings as regards food, liquid, and exercise, it is a much more difficult matter in their case to collect the bile without loss.

In Table II I have drawn up a series of averages which will help to elucidate my conclusions. Some of the estimations of the bile salts unfortunately miscarried, so that on several occasions the average of bile salts is for a less number of days than those on which a particular drug was given. This also applies in a few instances to the bile solids.

TABLE II.—Showing the average amount of Bile, Bile Solids, and Bile Salts on the days during which certain drugs or mineral waters were given.

Drugs Administered.	Quantity of Bile in c.cm.	Bile Solids.		Bile Salts.	
		Total in Grammes.	Per cent.	Total in Grammes.	Per cent.
Without medication	775	15.893	2.07	4.197	0.55
Old Sulphur Spring	878	18.584	2.14	5.870	0.69
Kissingen Spa	845	16.330	1.97	4.734	0.55
Carlsbad mineral water	809	18.352	2.24	5.560	0.68
Euonymin	836	17.360	2.03	5.031	0.60
Benzoate of soda	856	18.514	2.16	—	—
Salicylate of soda	797	17.215	2.14	5.462	0.68
Podophylloresin	744	18.714	2.48	5.774	0.73
Iridin	788	17.764	2.35	5.088	0.68
Chloride of iron spa	808	17.314	2.10	5.241	0.64
Strong Montpellier Sprin	747	15.318	2.00	3.853	0.50
Podophyllotoxin	758	14.311	1.88	4.044	0.56
Pint of hot water	785	16.519	2.09	4.207	0.53
Pint of soda water	783	16.612	2.10	—	—

INFLUENCE OF MINERAL WATERS.

The influence of the Harrogate mineral waters on the secretion of bile has never been tested experimentally, and as I am interested in this particular branch of therapeutics I began the investigation with them. It should be stated that the waters were sent up to London in bottles and kept in the laboratory some time before being used.

The Old Sulphur Spring.—The strong sulphur water generally acts as a mild laxative. If the bowels are moved naturally once a day the only difference it causes as a rule is that the evacuations are more copious, and this was the effect upon my patient. An average of four days gave 878 c.cm. of bile, with 18.5 g. solid. There is no doubt that this water has a very decided effect on the secretion and composition of bile, and I shall show in another paper that this effect is due to stimulation of the hepatic cells. As this water contains sulphuretted hydrogen gas it is possible the effect would have been greater had it been taken at its source.

No other drug or mineral water with which I experimented produced such a striking increase in both the quantity of bile and bile solids as the Old Sulphur Spring.

Strong Montpellier Spring.—The average of five days shows a diminution in the quantity of bile, in the solids, and bile salts, therefore this water is not a cholagogue. Hunter, in Allbutt's *System of Medicine*, asserts that the beneficial effects of most of the natural mineral waters are due to a flushing out of the biliary system. In the face of this and other experiments it is difficult to see how his hypothesis can be maintained.

Kissingen Spa.—The average of four days shows a distinct increase in the quantity of bile and a slight increase in the solids. The patient had a sharp attack of flatulent dyspepsia one night when he was taking this water, which necessitated the administration of two small doses of brandy. If this day's secretion be omitted, the average rises to 875 c.cm. of bile, with 16.6 g. solids; therefore, the action of the Kissingen water is to increase considerably the quantity of bile without materially augmenting the total solids.

Chloride of Iron Spa.—This water is prescribed for cases of anæmia. It was given to test the alleged effect of iron in reducing the quantity of bile. It should be stated, however, that in addition to iron it contains a large quantity of chloride of sodium, and appreciable quantities of the chlorides of calcium, magnesium, barium, and potash. The dose given was much larger than usual, but it did not disagree. The average of 808 c.cm. is somewhat misleading. The day before commencing the water the quantity of bile was 820 c.cm., and the day after it was stopped the quantity rose to 864 c.cm., and the solids to 19.457 g. It was my intention to have repeated this experiment, but time did not permit. The marked rise both in the quantity and the solids on the day after the last administration is a feature of interest.

In regard to the Harrogate waters, it is a point of clinical interest that the relative empirical reputations of the Old

Sulphur and the Strong Montpellier Springs are experimentally sustained.

Carlsbad Mineral Water.—The patient took 10 oz. before breakfast and 10 oz. at bedtime. The second dose purged him seven times. The next day he had 6 oz. before breakfast and 4 oz. at bedtime. The average of the two days gave 809 c.cm. of bile and 18.3 g. solids. The quantity would be higher were it not for the depletion produced by the purging. Notwithstanding the negative results obtained by other investigators, I have no hesitation in saying that the high esteem in which this mineral water is held as a cholagogue is undoubtedly deserved.

Water before Breakfast.—A pint of hot water before breakfast. This was given on one occasion. The result was 785 c.cm. of bile, with 16.5 g. solids. A pint of soda water before breakfast. This was also taken on one occasion. The result was 783 c.cm. of bile, with 16.6 g. solids. In both instances the quantity of bile was scarcely affected, but there was a very slight increase in the solids.

Euonymin.—The average of five days gave 836 c.cm. of bile, with 17.3 g. solids, but this does not convey an accurate idea of its effect in relation to the quantity. The patient took 12 gr. on the first day, which purged him six times, with a consequent diminution in the quantity of bile, which spoils the average. It is interesting to note that the solids were the highest on this day. On the last two days the drug was taken the quantity was 940 c.cm. and 904 c.cm. respectively, a very considerable increase; therefore euonymin unquestionably increases the quantity of bile, and, to a less extent, the bile solids.

Iridin.—The average of four days gave 788 c.cm. of bile, and the average of two days, 17.7 g. solids. From a consideration of these figures one can safely say that iridin does affect the complex chemical processes which take place in the liver without increasing the quantity of the bile.

Benzoate of Soda.—This drug was exhibited on one occasion, and in one dose of 20 gr. The result was 856 c.cm. of bile, with 18.5 g. solids. It is undesirable to express an opinion regarding the efficacy of a drug from merely one observation, but I should like to point out that the considerable rise in the total solids can scarcely be regarded as a coincidence, because during the days without medication the solids never exceeded 17 g.

Sodium Salicylate.—An average of two days gave 797 c.cm. of bile, with 17.2 g. solids, and the day after the discontinuance of the drug the solids rose to 18.3 g.; therefore there can be no doubt that it does influence the metabolism of the liver. During its administration the patient suffered a part of one day from indigestion, which might possibly have inhibited the biliary secretion. With one exception (Niessen) all investigators are agreed that this substance increases the secretion of bile.

Podophylloresin.—This is a resinous substance extracted from podophyllum emodi by Professor Dunstan,⁴² for a sample of which I am indebted to Dr. Dixon. It was given in non-purgative doses. The average of two days gave 744 c.cm. of bile, with 18.7 g. solids. This is rather misleading as regards quantity. The day before the drug was given the quantity was only 670 c.cm., the first day of administration 710 c.cm., the second day 779 c.cm., and the day after its discontinuance the quantity rose to 817 c.cm., with 17 g. solids. The increase in the solids is the highest of all substances tested, therefore I think this drug has a decidedly stimulating effect on the liver.

Podophyllotoxin.—This is another extract of podophyllum emodi, also extracted by Professor Dunstan.⁴² It was given on one occasion, and although the doses were supposed to be non-purgative it acted twice on the bowels. The result was 758 c.cm. bile, with 14.3 g. solids, and the day after the solids fell to 13.9 g., the lowest during the investigation, consequently this substance seems to have an adverse influence on the biliary secretion.

ANALYSIS OF THE URINE.

It was not deemed desirable to ask the patient to bring his urine until he became familiar with collecting his bile. The object in analysing the urine was to obtain an approximate idea of the amount of nitrogen excreted, and thereby an indication of the quantity of nitrogenous food assimilated. This end

could be more accurately attained by adopting some modification of Kjeldahl's process, but I wished to ascertain the action of the drugs used on the excretion of urea and uric acid. Unfortunately, the urine was frequently either neutral or faintly acid, so that conclusions drawn from the results obtained would probably be fallacious. Various expedients were tried to prevent its decomposition, but without much success. The quantity of urine was above the average—about 2,000 c.cm., and the specific gravity rarely exceeded 1010. The colour, considering the quantity, appeared to be normal. Although it was examined repeatedly for albumen no trace was detected.

For the estimation of urea Hufner's hypobromite method was employed. For estimating uric acid Hopkins's long process was used until January 7th, when I tried Otto Folin's modification of Hopkins's short method. This consists essentially in substituting 10 g. of ammonium sulphate for saturation with ammonium chloride in 100 c.cm. of urine, and subsequently washing the precipitate with a 10 per cent. solution of ammonium sulphate instead of a saturated solution of ammonium chloride. Folin's method is expeditious, but I do not think it is reliable when the urine is concentrated, and it was found with the dilute urine of my patient that two hours were insufficient for complete precipitation. The uric acid was observed to be increased while the patient was taking salicylate of soda, and, to a slight extent, during the administration of euonymin. Noel Paton found that euonymin increased while salicylate and benzoate of soda markedly diminished the excretion of uric acid. Hopkins, in Schäfer's *Physiology*, states that the salicylates undoubtedly increase the quantity of uric acid in the urine.

For estimating creatine Johnson's method was adopted, but a very small amount of the mercurial compound always adhered to the flask, hence a margin of error is introduced into the result.

For the estimation of ammonia Schloesing's method was adopted, but it is unsatisfactory for clinical purposes because of the length of time required. As the urea kept persistently below the normal in this case, it was considered probable that the ammonia would be increased in consequence of the diminished formation of urea. Neubauer found the quantity of ammonia to vary in health from 0.3 to 1.2 g. in the twenty-four hours, and this has been confirmed by later observers. In my patient it varied from 1.04 to 1.4 g., but it is doubtful whether this slight augmentation is due to the feeble reaction of the urine or to diminished functional activity of the liver.

SUMMARY OF CONCLUSIONS.

1. The amount of bile secreted in the twenty-four hours in a man somewhat below medium height and weight averages 775 c.cm. and the bile solids 15.8 g.
2. More bile is secreted during the day than at night.
3. The sulphocyanate of potash in the saliva is not derived from the biliary salts.
4. The following substances increase both the quantity of bile and bile solids—Old Sulphur Spring (Harrogate) Carlsbad mineral water, euonymin, benzoate of soda, salicylate of soda, and Kissingen Spa (Harrogate).
5. Podophylloresin and iridin augment the bile solids without appreciably affecting the quantity of bile.
6. Strong Montpellier Spring (Harrogate) and podophyllo-toxin appear to diminish slightly both the quantity and the solids.
7. Hot water and soda water in pint doses do not seem to increase the biliary secretion.
8. Salicylate of soda increases the excretion of uric acid in the urine.

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THE EFFECT OF EXERCISE ON THE HÆMOGLOBIN WITH REFERENCE TO THE VALUE OF REST IN THE TREATMENT OF ANÆMIA.

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The observations made by G. Oliver and the writer, and published by the former in the Croonian Lectures for 1896,¹ have shown the occurrence of a diurnal physiological variation in the blood of healthy subjects, a fall in the percentage of hæmoglobin, corpuscles, and of the "worth" of the corpuscle taking place during the day, and a rise during the night.

Chart 1, taken from a continuous chart of observations on another subject is a typical example of the normal daily variations.