A Paper

ON

SOME PHARMACOLOGICAL EFFECTS OF THE
STRONG SULPHUR WATER (HARROGATE).

BY

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[AFTER expressing his thanks for the opportunities afforded him of bringing his laboratory results to the notice of the societies, Dr. Brown proceeded:]

The results obtained in various clinical cases of gout kept under close observation, during their treatment by the strong sulphur water of the Harrogate Spa, induced me to institute a special plan of research into the pharmacological action of this water on the following cases:

1. In a normal adult (length of experiment, 42 days).
2. In an adult where some slight variations from normal metabolism were suspected (length of experiment, 19 days).
3. In a case of simple acute gout of eight weeks' duration, and not previously treated by drugs or other means (length of experiment, 16 days).

The points considered and methods employed were:

1. Amount and specific gravity of urine.
2. Total nitrogen of the urine (Kjeldahl).
3. Total daily excretion of uric acid (Hopkins).
4. Total daily excretion of xanthin bases (Ludwig Salkowski).
5. Total daily excretion of kreatinin (Folin).

The observations were made daily on the massed total excretions of urine of the previous twenty-four hours.

No chloroform or boiled or otherwise preserved specimens were used.

The calculations are correct to 5 c.cm. of urine. No collection of urine was used which was of a greater age than four hours.

Before the work was started the plan and scope of the inquiry received the valuable criticism of Dr. Gowland Hopkins of Cambridge.

As the work was done without collaboration, the following method was adopted, in order that the personal equation of the experimenter might be eliminated as far as was possible:

1. No calculations were even roughly worked out during the progress of the experiments.
2. At the close of each series of experiments the results of each series of observations were independently calculated and charted.
3. Lastly, the charts of the various cases were contrasted and compared.

CASE I.

Conditions of Experiment.—Length of experiment forty-two days, divided into five distinct periods (1-5). Date of commencement, November 10th, 1909.

Period 1, of nine days, on unlimited non-purin diet.

Period 2, of nine days (9-18 inclusive), on limited and fixed non-purin diet. This diet was continued through the remainder of the experiment. The diet contained a daily average of 3,200 calories; its constituents were as follow: Milk 26 oz., butter 2½ oz., cream 1 oz., bread 17 oz., eggs 5, cheese 1½ oz., macaroni 2 oz., rice ½ oz. Aërated distilled water 30 oz. (It was the usual habit of the experimentee to use this last in lieu of ordinary drinking water.)

Period 3, of thirteen days (19-31). Strong sulphur water was taken in addition to the diet detailed in Period 2.

The doses taken daily were:

Nineteenth day of experiment	...	20 oz.
Twentieth day of experiment	...	12 "
Twenty-first day of experiment	...	16 "
Twenty-second day of experiment	...	18 "
Twenty-third to thirty-first day of experiment	...	20 "

The smaller doses taken were due to the fact that the dose taken on the nineteenth day caused more than one fluid motion, and it seemed probable that certain excretory effects might possibly be hidden by the free purgation.

Period 4, of nine days (32-40). Same diet was taken as in Period 2.

*Read before the Harrogate Medical Society (March 17th, 1910), the Cardiff Medical Society (April 12th, 1910).

Period 5, of two days (41-42). The same diet was continued, but unusual exercise (walk of eight miles through deep snow) was taken on the forty-first day.

Also at 5 p.m. on the fourteenth, twenty-seventh, and thirty-sixth days of the experiment respectively a dose of 0.5 gram of pure hypoxanthin (Merck) was taken in cachets. This dose of hypoxanthin corresponds roughly to that found in 2½ lb. of mutton (Hall's tables). The further details of the conditions of the experiment are appended.

Exercise.—An amount limited to about three miles per diem of walking exercise was taken daily. On the three days on which the doses of hypoxanthin were given no walking exercise was allowed, so that any possible chance of only a partial absorption of the full dose of hypoxanthin might be avoided, such as might have occurred if the bowel had been evacuated more than once each day. A daily average of fourteen hours was spent in laboratory work, except on the forty-first day, when the unusual exercise was taken.

Rest.—About six and a half to seven hours per night was spent in bed.

Temperature.—Work was undertaken in a laboratory, which had three windows constantly open, and was without heat, except that of the necessary Bunsen burners. Additional clothing was worn to prevent undue tissue waste in keeping up the heat of the body in this low temperature (November and December).

Bowel.—Opened once daily about 9.30-10 a.m. on each day of experiment, except on the nineteenth day (first day of taking sulphur water), when the bowel was opened three times. No recourse was made to laxative drugs during the whole period of the experiment. On the seventh and eighth days of the experiment there was some slight constipation, and five apples were eaten on the seventh day. On the seventh and eighth days there was, as we shall see, an abnormal excretion of uric acid, due to the constipation or to some effect of this addition to the diet.

Body Weight.—This was taken at the commencement of the experiment, and measured 10 st. 6½ lb. It was repeatedly taken during the course of the experiment, and no variation of more than ½ lb. was at any time noticed, except that on the thirty-second day the weight was 10 st. 7½ lb.

The final weight, after the short period of unusual exercise, was 10 st. 4½ lb.

It is especially important in all xanthin base (purin) and uric acid estimations that the body weight should be stationary, otherwise with a falling body weight one has to admit the possibility of excessive tissue waste and a consequent rise in the amount of endogenous purin excretion.

The results of the experiment were as follows, and are shown graphically in detail in Charts A, B, C, D, and C".

The dotted lines in the various charts denote the average amount of excretion of a given substance in the given period concerned.

You will notice that there are occasional gaps in the series of results. This is due to the fact that all results which did not seem to be quite perfect from a technical point of view were invariably rejected. The methods used for the estimations were those which, though often laborious, appear to be able to give the most nearly constant results.

CHART A.—Urine Measured in Cubic Centimetres.

Period 1.—Urine varied considerably. This was probably connected with the variable amount of nitrogenous

food taken during this period, and perhaps the slight constipation noticed had some effect.

Period 2.—Less variation in daily amount. Average amount, 900 c.cm.

Period 3.—Considerable diuresis noted. Average amount of urine, 1,260 c.cm. Diuresis amounted to 40 per cent. compared with Period 2. This diuresis reached its maximum on the seventh day of administration of sulphur water (the twenty-fifth of the experiment); the amount after this gradually decreased.

Period 4.—Average daily amount, 1,020 c.cm. There is a gradual fall in the daily amount during this period, the amount being less than that of Period 2, on the fifth and succeeding days, following the cessation of the administration of the sulphur water.

Period 5.—The urine was further contracted in amount, a result probably due to loss by perspiration.

Specific Gravity of Urine (lower line of Chart A).—The specific gravity of the urine in detail varies inversely with the amount of the urine from day to day, but the average specific gravity during Period 3 is nearly as high as in the pre-sulphur periods, showing that sulphur water increases the total solids of the urine.

CHART B.

The total nitrogen of the urine was taken throughout the whole period of the experiment, but is only of value for our purpose in so far as it concerns the periods of fixed diet (2-5).

Period 2.—It remained steady, at an average of 13.2 grams per diem—that is, nearly $\frac{1}{2}$ gram per kilo of body weight, or 19 grains per stone.

Period 3.—Raised about 10 per cent.

Period 4.—Only fractionally lower than in Period 3. This sustained excretion in the post-sulphur stage is very interesting, and with the body weight remaining constant, while the feeding also was constant, can only, I think, be explained on the supposition that increased absorption of nitrogen took place, and was accompanied by acceleration of body-tissue change.

Period 5.—The daily average was further raised. This was due to the increased exercise on day 41.

CHART C.—Uric Acid and Xanthin Bases.

Burian and Schur proved conclusively that no variation in the amount of nitrogenous intake had any effect so long as the nuclein containing elements of food, that is flesh, were avoided. Their variations in dietary ranged from twenty-four eggs to four eggs per diem, and the urea excretion varied correspondingly and enormously, but the uric acid and other purin excretion remained constant. Hypoxanthin only differs in constitution from uric acid by two atoms of oxygen and xanthin by one such atom, and these are probably the immediate precursors in the body of the most highly oxidized member of the series, that is, uric acid. The adenin and guanin by the action of ferments lose their amido groups and are oxidized to hypoxanthin and xanthin respectively. While all the bases appear in the urine during a non-purin diet, the principal purin body excreted other than uric acid is hypoxanthin; this is one main reason why hypoxanthin bases were administered, as

has been described, in order to test the effect of sulphur water on the *exogenous* purin excretion.

Perhaps I may recall Folin's researches which finally divided uric acid and xanthin excretions into the portion coming from body tissue change (*endogenous*) and that derived from the food (*exogenous*). Burian and Schur showed that the *exogenous* purin excretion in man amounted to about 50 per cent. of the xanthin bases of the food, and was excreted as uric acid, the rest being destroyed and probably excreted as urea. Later observers, and especially Ackroyd, have shown that the 50 per cent. statement is too rigid. On the other hand, the excretion of *endogenous* uric acid and xanthin bases is peculiar for each person, and is constant, or nearly constant, for the individual. In estimating the uric acid and xanthin bases 500 c.cm. of the daily massed urine was taken when the amount for the twenty-four hours was 1,000 c.cm. or less. When the total amount of the secretion permitted it, the experiments were done in duplicate, often as much as three quarters of the total days' urine being used, for the estimation of the uric acid and xanthin bases. Where the urine

URIC ACID AND XANTHIN BASES.

IN MILLIGRAMMES
NITROGEN.

CASE 1

CHART C.

deposited crystals of uric acid these were separately treated.

The upper line shows the uric acid excretion (Chart C), calculated as nitrogen.

Period 1.—Average 120 mg. This was disturbed by constipation on days seven and eight, and so the whole period is neglected.

Period 2.—Average excretion of the first four days is 115 mg. nitrogen (= 345 mg. uric acid).

Period 3.—Average excretion for seven out of the first eight days of this period is 123 mg. nitrogen (= 370 mg. uric acid).

Period 4.—Average excretion of first four days of this period is 134 mg. nitrogen (= 402 mg. uric acid).

Therefore the rise in Period 3 equalled 8 per cent., and the rise in Period 4 a further 11 per cent.—a total rise of nearly 20 per cent. in the excretion of *endogenous* or body tissue uric acid.

Exogenous Uric Acid (0.5 gram hypoxanthin).—This is represented by the blackened areas of the chart in Periods 2, 3, and 4. On each occasion the $\frac{1}{2}$ -gram dose of hypoxanthin was given at 5 p.m. It was given thus late in the day to allow of the absorption of the hypoxanthin undisturbed by possible accidental movements of the bowels during Period 3. (The precaution proved to be unnecessary.)

Period 2.—36 per cent. of the hypoxanthin recovered as uric acid.

Period 3.—80 per cent. of the hypoxanthin recovered as uric acid.

Period 4.—40 per cent. of the hypoxanthin recovered as uric acid. This last result is almost identical with that obtained in Period 2.

The length of time necessary for the excretion in Period 2 is *three* days. In Periods 3 and 4 this is much shortened, being only *two* days. This, again, is an indication of greater tissue ferment activity.

The lower line in Chart C shows the excretion of the xanthin bases, or, as they are more often, though less correctly, termed, "the purins." These are calculated as nitrogen.

Period 2.—Average for first four days of period is 19.5 mg. nitrogen (=nearly 60 mg. of hypoxanthin).

Period 3.—Average for first eight days is 13.2 mg. nitrogen (=nearly 40 mg. of hypoxanthin). This is a fall of 33 per cent.

Period 4.—Average for first four days is 10.5 mg. nitrogen (=nearly 31 mg. of hypoxanthin). This is a further fall of 22 per cent.

The results of the whole analysis are better seen in Chart C", where the ordinates are three times as long as in the Chart C. In Chart C the xanthin base excretion is on the same scale as that of the uric acid nitrogen, in order to show their relative amounts.

On Chart C" the dark patches represent the excretion of the purin bases during the periods when the hypo-

xanthin taken by the mouth was in part being excreted in varying percentages as uric acid.

The purin base excretion on the three such occasions was not increased, but either below or only just above the average for the earlier days of the particular periods concerned (2, 3, 4).

Hence there is no evidence that any of the *exogenous* hypoxanthin taken by the mouth escapes as such.

In other words the diuresis which is marked when taking sulphur water is in no way able to cause extra excretion of the not fully oxidized purins (xanthin bases).

The action of sulphur water on purin metabolism, even on those purins which are soluble (ex hypoxanthin), is other than that of a mechanical diuresis, or lowering of the flood gates, such as in all probability is the case in connexion with the increased uric acid output during treatment by the salicylates.

Another point in the chart (C) is the primary rise of *endogenous* (or tissue) uric acid on the first two days of ingestion of sulphur water. Also the curious exaggeration of the increased excretion of uric acid after the termination of the excretion of *exogenous* uric acid resulting from the ingestion of the hypoxanthin. Does the ingestion of a moderate amount of the free purin stimulate xanthin oxidase so that it can deal with a larger amount of *endogenous* purins? Also note the increased excretion of xanthin bases after the termination of the excretion of the *exogenous* uric acid. Is this the delayed excretion of the residue of the dose of *exogenous* purin? It is shown both in the pre- and sulphur stages (2 and 3).

Where and how is the extra transformation of the hypoxanthin to uric acid brought about? Xanthin oxidase in the liver is probably mainly responsible under ordinary conditions for the oxidation of xanthin bases to uric acid. And one is driven to the conclusion that some one or more of the constituents of or some physical or electrical condition of the sulphur water has a stimulating effect on this ferment. It is certainly startling to find that the diuresis caused by sulphur water has *no effect* whatever on the excretion of soluble purins as such. This is shown in Chart D.

Here, then, an explanation suggests itself of the assertion often made, and so puzzling to justify by what we

know of metabolism, that sulphur water first increases and then decreases the amount of the daily excretion of uric acid. The action of sulphur water is probably a double one as far as the purin bodies are concerned, and when the patient is on a fixed mixed diet:

1. The nuclear albumen of flesh food resists digestion longer than other proteids, and is swept out by the daily laxative action of the water in greater proportion than are other albumens. This is probably not the case when the subject is fed with soluble xanthin bases, such as hypoxanthin, this latter substance being usually well absorbed.

2. The actual tissue uric acid is increased, as shown in the charts, but this increase is not enough to balance the loss of purin-forming substances, which, under ordinary circumstances, are absorbed, but which are directly swept out of the intestine by the action of the sulphur water.

The ultimate proof of this view will be included in a subsequent paper dealing with the faecal purins.

CHART D.—Kreatinin.

Unfortunately the colorimeter which Dr. Dimmock kindly lent me, and which rendered possible this series

of observations, did not come into my hands until the seventeenth day of the experiment, so that the period for observation of the average endogenous kreatinin is short.

However, the amounts observed are about normal, the experimenter being of spare habit.

Period 2.—Average of two days is 2 grams.

Period 3.—Average excretion is 2.2 grams.

Period 4.—Average excretion is 1.9 grams.

Period 5.—Average excretion is 1.8 grams.

During Period 3 the excretion was markedly higher than in Period 4—that is, by 15 per cent.; while the excretion in Period 4 was on the average lower by 5 per cent. than in Period 2.

Further, the percentage relation to the total nitrogenous excretion was even more marked in Period 3 than in Period 4. This is shown on lower part of Chart D.

The numbers are: Period 3, 15.2 per cent; Period 4, 13.6 per cent.

CASE II.

In this case possibly some minor abnormalities of metabolism might be expected. Considerations of space preclude the reproduction of the charts comparable with those of Case I. The results obtained confirm those detailed in the former.

The conditions as to diet were similar to those of the first case, but every approximately non-purin containing food (by Walker Hall's tables) was permitted, and the diet was unlimited in amount during the whole period of experiment (nineteen days); 8 oz. of claret was taken daily with meals. Eleven days were spent on the preparatory non-purin diet; on the succeeding eight days 20 oz. of sulphur water was taken per diem, and the same constituents of the urine were daily examined by the same methods as in Case I. No restrictions as to exercise were made. Unfortunately, constipation was a trouble during the first stage, and had to be met by doses of cascara sagrada, and on one occasion by an enema.

This drug was chosen as being least likely to interfere with general metabolism, being held to be simply a pure muscle stimulant. This constipation, I am afraid, somewhat disorganized the purin metabolism, but still these charts in the main show the same results as in Case I. The solitary counter-result affects the total amount of nitrogen excreted, which was slightly higher in the first than in the sulphur-water stage; also very free evacuation of the bowel occurred on the first and second days of ingestion of sulphur water. The number of motions for the first four days was respectively 3, 2, 1, 2.

Uric Acid.—The endogenous uric acid shows a rise from an average of 107 to 115 mg. of uric acid nitrogen.

The Exogenous Uric Acid.—The two doses of hypoxanthin of $\frac{1}{2}$ gram each, taken on respectively the ninth and seventh days of the experiment at 5 p.m. in the afternoon, show the following results: In the pre-sulphur stage 50 per cent. was recovered as uric acid. And that taken during the treatment by sulphur water shows nearly 80 per cent. as additional uric acid. This result is almost identical with that obtained in Case I.

I may here note the very large deposition of uric acid crystals during almost the whole of the sulphur water taking stage. The xanthin base excretion shows fewer points than in Case I, but the average excretion is slightly lowered during the latter days of the second period as compared with the last four or five days in the pre-sulphur period. Here, of course, the disturbing influence of irregular exercise is apparent, especially on day 12.

The Volume of the Urine and the Specific Gravity.—The results obtained were similar to those noted in the first case, except that the diuresis was not so marked in the sulphur water taking stage, a circumstance due in all probability to the free purgation which followed the ingestion of the first two doses of sulphur water. The average excretion of water during the first stage was 1,175 c.cm., in the second or sulphur stage it was 1,420, an increase of rather more than 25 per cent.

Kreatinin.—The excretion of kreatinin in the pre-sulphur stage was found to be abnormally high. This, as I have already hinted, had been suspected at the commencement of the experiment. Case II is subject to recurrent migrainous headaches and to an abnormal condition of lassitude and depression following unusual exertion, and this is associated with a somewhat low blood pressure. The average excretion of kreatinin during the pre-sulphur stage was nearly 2.8 grams per diem. During the taking of sulphur water it rose to about 2.9 grams as an average, an increase of 5 per cent. The percentage relation of kreatinin to total nitrogen excretion is more striking, and the average percentage in the two periods was respectively 17 and 20. Weight remained stationary at about 11 st. 8 $\frac{1}{2}$ lb. during the whole experiment.

CASE III.

This subject was elderly, and had had repeated attacks of gout. He has a great prejudice against any drug treatment whatsoever. The present attack has lasted for nearly eight weeks. Typical swelling of foot and leg to level of patella. On his arrival he was put on an unlimited non-purin diet with 5 oz. of flesh food. He took this diet for four days before commencing sulphur water; on the third and fourth days observations were made as regards volume, specific gravity of the urine, and the total amounts of uric acid xanthin bases and kreatinin. Unfortunately, with regard to the last substance, one of the older mercury methods of estimation was employed, the results of which do not appear to be accurate and so are neglected.

1. *Amount and Specific Gravity of Urine (Chart A').*—The amount on the third and fourth days was respectively 500 and 520 c.cm. On the fifth day he took his first dose, 12 oz. of sulphur water, and continued to take this dose for the eleven succeeding days. The urine on the first day rose to 820 c.cm., and the average amount of urine for the whole of this period is about 1,075 c.cm., the diuresis more than doubled the total amount of urine. The pre-sulphur measurements probably show an unnaturally contracted output, as four days subsequent to the cessation of the taking of sulphur water the urine measured rather over 800 c.cm.

The specific gravity of the urine during the taking of the sulphur water does not vary inversely with the amount of the urine, as was the case in the two previous subjects examined, but is high, showing much increased excretion of solids.

2. *Uric Acid (Chart C', upper half).*—This shows, although the patient was taking 5 oz. of purin-containing food, a total no higher than in the two previous cases on a non-purin diet, and varied very little, except slightly in a downward direction, during the first seven days of the administration of sulphur water. On the eighth day of the administration of sulphur water the purin-containing elements of the diet were

increased from 5 to 8 oz. of flesh food, with the result, as far as the uric acid is concerned, which is shown on the chart. The amount of uric acid excreted per diem fell on the eleventh and twelfth days of the administration of sulphur water.

3. *Xanthin Bases (Chart C', lower half).*—The details on the chart are here, I am sorry to say, somewhat fragmentary. On four days the estimations suffered from some technical fault,

and so are omitted. The purin average is high during the first stage, but I think there can be no doubt about the general fall during the last five days, when the larger amount of

purin-containing food formed part of the diet. Here, then, is another suggestion that possibly the addition of purin-containing food or free purin may stimulate the oxidation of purin substances remaining in the body.

I do not wish to hide the fact that on the eighth day of administration of sulphur water the patient was much improved, and on the tenth day the swelling of the leg, which on his arrival in Harrogate reached to the knee, had nearly disappeared, so that a boot could be worn for the first time for nearly ten weeks. The extra amount of exercise may account somewhat for the increase in uric acid on the first three days of the increased diet.

Summary of Results.

In the briefest possible form the three cases show these results (compare Chart A of Case I with Chart A' of Case III, and Chart C of Case I with Chart C' of Case III):

	Case I.	Case II.	Case III.
1. Amount of urine ...	+40 per cent.	+25 per cent.	+110 per cent.
2. Specific gravity of the urine	Tends to vary inversely with the amount of the urine passed from day to day, but is relatively higher during the taking of sulphur water, showing increased excretion of total solids		Tends to vary directly and not inversely on certain days, tending to show very large increase of excretion of total solids in cases of gout.
3. Excretion of total nitrogen	+10 per cent.	Result uncertain or negative	Not observed.
4. Endogenous (or body) uric acid during taking of sulphur water	+8 per cent.	+5 per cent.	Low during the treatment.
5. Endogenous (or body) uric acid after cessation of taking sulphur water	+ further 11 per cent. (in all nearly 20 per cent. increase)	—	—
6. Percentage of 0.5 gram of hypoxanthin taken by mouth obtained as uric acid	36 to 40 per cent.	50 per cent.	—
7. Increased percentage of hypoxanthin during taking of sulphur water	To 80 per cent. nearly	To 80 per cent.	—
8. Decrease in excretion of endogenous xanthin bases during treatment with sulphur water	-33 per cent. (with fixed amount of exercise)	Slight decrease (exercise unlimited)	—
9. Decrease in excretion of endogenous xanthin bases after sulphur water	Further -22 per cent. (total fall 45 per cent.)	—	—
10. Endogenous kreatinin during taking of sulphur water	+5 per cent.	+5 per cent.	—
11. Endogenous kreatinin after cessation of treatment	-10 per cent.	—	—

No increase in excretion of xanthin (purin) bases as such results from taking of sulphur water in conjunction with doses of *exogenous* pure purin (hypoxanthin).

GENERAL RECAPITULATION.

Now for a general recapitulation. Sulphur water has in the main an oxidizing action on the products of metabolism. It also probably prevents the usual amount of absorption of nucleo-albumens by its action on the intestine. In detail the results obtained are:

1. In physiological subjects there appears to be an increase in the excretion of total nitrogen, probably dependent on an increased general metabolism.

2. The *endogenous* uric acid during the taking of sulphur water and subsequent to that period is increased in all by 20 per cent.

3. The excretion of *exogenous* purins, as tested by taking measured doses of a pure xanthin base, is increased, as is shown on the chart. The increase in the amount of uric acid excreted and due to this source rises from 40 to 80 per cent. of the total amount of *exogenous* purin material ingested.

4. Sulphur water has no power to increase the amount of xanthin bases excreted as such.

5. The excretion of *endogenous* xanthin bases is during the period of ingestion of sulphur water approximately decreased by 33 per cent., and in the post-sulphur stage

there is a further diminution in excretion, which reduces the daily excretion of *endogenous* xanthin bases to little more than half of the daily excretion in the pre-sulphur stage, when the subject was on a fixed non-purin diet.

The results point most strongly to a stimulation of xanthin oxidase as a result of treatment by sulphur water. The second case shows results which are comparable with those of the first case. The *third case*, that of gout, with regard to uric acid, shows the total excretion of only the same level as that seen in the first case on a measured non-purin diet, in spite of the 5 oz. of meat food included in the diet. It also shows an increase in the total amount of uric acid excretion following the further addition of 3 oz. of meat to the diet, which for amount compares roughly with that seen in the sulphur period in Case I. With regard to the xanthin base excretion, this is during the whole of the sulphur water period unduly high, until the last few days of that period, when rapid amelioration of the gouty condition was taking place, when there was, in spite of the addition made to the diet, a sudden and sustained fall in the amount of xanthin base excretion.

6. *Kreatinin*.—The combined results of Cases I and II tend to show that an increase in excretion takes place during the period of ingestion of sulphur water, and a fall subsequent to this period, amounting in Case I to 15 per cent. This fall subsequent to the period of treatment with sulphur water is noteworthy when we recognize that the total excretion of nitrogen does not correspondingly fall. These results are probably dependent on the setting up and lessening of the cessation of the diuresis.

7. *Amount of Urine and Specific Gravity*.—Considerable diuresis appears to occur in physiological cases—a diuresis even more marked in the pathological case (gout), where one had some reason to suspect an abnormal contraction in the volume of the urine before the treatment was commenced.

The Specific Gravity.—The lowering of this did not correspond with the degree of diuresis during the treatment with sulphur water, and tends to uphold the view that sulphur water leads to an increase in the excretion of the total solids. The third case, indeed, on certain days, shows an increase in the specific gravity, in spite of the large increase in the total volume of the urine. This suggests that retention of incompletely oxidized products of metabolism occurs in acute gout.

I have to acknowledge my indebtedness for advice and encouragement to Dr. Gowland Hopkins and Dr. Ackroyd of Cambridge, to Dr. Dimmock for the loan of apparatus; also I have to express my obligations to Dr. Solly for a very practical sympathy with this inquiry; to Dr. Mantle of Harrogate; to Mr. Rivers, the borough meteorologist, for working out some statistics; and, last but not least, to Mr. Eynon, pharmacist of this town, who, when I was most pressed with laboratory work, prepared and standardized test solutions which, for want of time, I could not myself undertake.

I have to thank you, Mr. President and Gentlemen, for this opportunity of detailing to you the results of many months of work, and I can only wish that my interest in this inquiry may, to a certain extent, infect you and lead to a very lively discussion.

[After the reading of the paper in Harrogate a discussion followed, in which Drs. Black, Edgecombe, and Solly took part.

At Cardiff a discussion of various points raised by the paper ensued, in which Mr. Tennyson Collins (President, Cardiff Medical Society), Drs. Scholberg, Mackenzie Wallis, Treasure, Cresswell, and other gentlemen joined.]

WE gather from the latest report of the Church of England Mission of Hop-pickers that last year the number of temporary immigrants into Kent was as high as 50,000. It is not only for their spiritual needs that the mission caters, makeshift hospitals and trained nurses and like provision being made. The enterprise which started some 43 years ago with four workers now demands the services of over 150 persons. This need is readily comprehensible, as the immigrants are spread over a wide area. Although most of the workers give their services, the expenditure is necessarily considerable. Donations may be sent to the Rev. F. G. Oliphant, Rector of Teston, Maidstone. Request is also made for sound illustrated literature, and old linen for bandages, parcels being sent to Watlington station.