possibly prevent some soiling of the linen and the possible spread of infection if the case be one of typhoid bacilluria. In hospital practice, however, with good nursing, the matter is of less importance. In private practice among the poor the case is very different. Since in all probability in such cases, as I have elsewhere pointed out, the urine rather than the faeces is chiefly at fault, it is permissible to hope that by eliminating the former source of danger altogether a very sensible diminution in the spread of the disease may in time be brought about.

[In an appendix to his lecture Dr. Horton-Smith gave the exact details concerning four cases of typhoid bacilluria and cystitis treated with urotropin. These demonstrated clearly that if the drug be given for a week (10 grains three times a day), an almost certain cure of the condition can be brought about. Often, indeed, much smaller amounts were in reality sufficient.]

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THE ACTION OF VARIOUS DRUGS AND DIETS ON THE EXCRETION OF NITROGEN IN GOUT.*

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THE study of the elimination of nitrogen in gouty cases is of special importance on account of the relationship which uric acid holds to gout, and the consequent view that gout is essentially a disease of disordered metabolism. The object of this series of observations was to determine, if possible, the variations in nitrogenous elimination occurring in a case of gout under ordinary conditions, and to note the effect of different diets and certain drugs. For this purpose urea, uric acid, alloxur base, and ammonia were all separately determined—the urea to serve as a measure of the total nitrogenous changes—the uric acid and alloxur base as a possible sign of modified production of these bodies, and the ammonia as an indication of the general amount of inorganic acid dealt with during the day's metabolism. There are two alleged sources of uric acid:

1. It may be a derivative of the alloxur base combined within the molecule of the nucleo-proteid of cells, or similar substances in the food.

2. It may be produced by synthetic processes in the liver or elsewhere from simpler nitrogenous compounds such as ammonia.

If the former view be the correct one, variations in the amount of uric acid excreted must simultaneously produce variations in the final waste products resulting from the disintegration of nucleo-proteid, one of which—phosphorus—we can follow. For this reason the phosphorus pentoxide excretion was also determined, but it must be remembered that the main amount of phosphates excreted in the urine has been derived from the phosphates taken as such in the food. The amount of ammonia excreted has been shown to depend

largely, if not entirely, on the excess of mineral acid over fixed bases available, and consequently fluctuations in its amount follow variations in the diet.

I am indebted to Dr. Barrs for the opportunity of investigating the following case of chronic gout:

G. D., aged 65, a well-built man, 6 feet in height and weighing 12 st. 4 lbs., who followed the curious vocation of tailor and dancing master, was readmitted into the Leeds General Infirmary on November 2nd, 1899. His family history revealed little of positive importance. An uncle had suffered from gout; but while his father, dying at the age of 67, was believed to have shortened his life by over-indulgence in alcohol, he had never been affected by gout. There was, however, a history of rheumatism in his case. The patient's mother, aged 77, at the time of her death, was always free both from gout and rheumatism. The patient's past record was excellent. Apart from the affection for which he was admitted, and an attack of erysipelas twenty-three years previously, his health had been very good. The history of gout covered five years. At the beginning the patient attributed the swelling of the joints to the fact that his feet ceased to perspire profusely. The recurring attacks were ushered in by shooting pains, the joints becoming red, swollen, and very hot. These symptoms gradually subsided after two or three days, with exception of the swelling, which persisted. At the time of readmission his general health was good, and no disease of internal organs could be discovered. Gouty changes were marked both in the hands and feet, the enlargement due to deposits being indeed extreme. In the hands the metacarpo-phalangeal and first interphalangeal joints were mainly affected. The dorsum of the left wrist was occupied by a considerable swelling. The elbow of the same arm was affected at two points, there being a very hard swelling in connection with the ulna, and a softer one forming a cushion-like expansion of the apex of the joint. At the back of the internal condyle of the other elbow-joint was a nodulated enlargement equaling a filbert in size. The fifth metatarsal joint of the left foot showed a large hard swelling, and a similar enlargement existed on the outer side of the fifth toe, with a smaller one on the dorsum of the fourth. The lower part of the tendo Achillis was irregularly swollen. The small toe of the right foot was enlarged dorsally, a smaller swelling affecting same surface of the first and fifth tarso-metatarsal joints. The tendo Achillis was in a condition similar to that described in the case of the left foot. The patient stated that the joints gave rise to no pain, except when at long and irregular intervals an inflammatory condition supervened.

The case was interesting from the fact that although the first manifestations of gout presented themselves only five years before, the deposits described were so large as to render it almost unique. A feature of interest, from an etiological point of view, was the abstemiousness of the patient combined with his active habits. Except for a slight hereditary taint no possible clue in relation to its causation was obtainable. The urine, repeatedly examined, was free from albumen, albumose, and peptone; and throughout the investigation was acid in reaction.

Methods of Analysis.—The urea was estimated by the hypobromite method and uric acid both by Hopkins's and Salkowski's processes. Schlösing's method was adopted for ammonia and titration by uranium nitrate for the P_2O_5 . The alloxur bases were estimated by Salkowski's recent method described in a former paper on gout.

While under observation the patient was placed on the subjoined diets:

Fixed Diet.—Cocoa 1 pint, tea 2 pints, milk 1 pint, tea cake 2 oz., bread 11 oz., butter 1 oz.; dinner, 1 lb. 6 oz., including 4 oz. of meat and 1 apple.

Vegetable Diet.—This consisted to a large extent of peas and beans. Milk 1 pint, oatmeal porridge $\frac{1}{2}$ pint, pea soup $\frac{1}{2}$ pint, peas porridge $\frac{1}{2}$ pint, bread 11 oz., butter 1 oz., peas, beans, and other vegetables 1 lb. 8 oz.

Animal Diet.—Milk $\frac{1}{2}$ pint, lemonade 1 pint, meat 10 oz., bread 10 oz., butter 1 oz., potatoes 4 oz., and 1 apple.

In addition to being dieted, the patient took the same amount of exercise each day.

The results obtained are tabulated on p. 835.

Referring first to the estimations made before the administration of drugs and the adoption of experimental diets—that is to say, under ordinary conditions—it will be observed that the fluctuations were well within physiological limits with the exception of urea, which was somewhat low, a common feature in connection with hospital patients, resulting, of course, from the small quantity of nitrogenous food taken; but in this case the alternative possibility of a nitrogen retention must be borne in mind. Taking into consideration the patient's age, the uric acid excretion must be regarded as normal. The bases also bore the usual relationship to uric acid. The estimation of the bases gains much interest from the important researches of Minkowski, who administered adenin to four dogs in doses varying from 0.25 to 0.5 gram several times a day. Three of the animals were killed about the fourth day, and the other died on the second day. After 2 grams vomiting ensued, and the other symptoms noted were violent action of the heart, a heaving pulse, and an increase in blood pressure. The urine contained albumen, leucocytes, casts, and epithelial cells. *Post mortem* crystals of biurate were found deposited in the convoluted and Henle's tubules, but not in the glomeruli. There was also cellular infiltration of the connective tissue.

It is certainly striking that this train of symptoms, with

* Read before the Medical Society of London.

TABLE I.—Showing the Analytical Details of the Urine in the 24 Hours.

Date.	Diet.	Drugs.	Total Quantity in c.cm.	Specific Gravity.	Urea in Grams.	Uric Acid in Grams.	P ₂ O ₅ in Grams.	Alloxur Bases in Grams.	Ammonia in Grams.	Remarks.
Nov. 3	Fixed diet.		1720	1011	17.200	0.401	1.21	0.055		Temp. normal.
" 4	"		1420	1013	18.460	0.367	1.27	0.051		
" 5	"		1360	1014	21.760	0.480	1.37	0.061		
" 6	"		1430	1012	19.305	0.509	1.51	0.067	0.486	
" 7	"		1095	1018	18.615	0.409	1.20	0.050		
" 8	"		1535	1013	20.327	0.457	1.41	0.057	0.582	
" 9	"		1435	1015	21.455	0.476	1.48	0.048		
" 11	"		1380	1017	20.735	0.545	1.57	0.053	0.455	
" 12	"	{ Sodium salicylate } 20 gr. ter die	1555	1017	24.824	0.529	1.59	0.075	0.509	
" 13	"		1600	1015	21.612	0.491	1.56	0.075	0.489	
" 14	"		1170	1019	20.061	0.544	1.70	0.058	0.457	
" 15	"		1330	1015	19.951	0.449	1.31	0.060		
" 16	"		1673	1012	20.076	0.601	1.68	0.061	0.615	
" 17	"	{ Guaiac. resin, 18 gr. } ter die	1900	1010	19.164	0.600	1.44	0.054	1.113	
" 18	"		1800	1010	17.864	0.708	1.36	0.051	0.724	
" 19	"		1320	1012	17.820	0.842	1.18	0.053	0.516	
" 20	"		1850	1014	20.905	0.749	1.38	0.057	0.757	
" 21	"		1495	1013	20.115	0.688	1.61	0.059	0.685	
" 22	"	{ Potassium iodide, } 5 gr. ter die	1655	1013	23.170	0.606	1.45	0.058	0.787	
" 23	"		1505	1013	21.070	0.547	1.44	0.052	0.613	
" 24	"		1733	1012	23.048	0.571	1.59		0.561	
" 25	"		1620	1015	24.312	0.701	1.62		1.046	
" 26	"		1230	1015	24.986	0.618	1.75		0.701	
" 27	"		1002	1015	19.038	0.453	1.48		0.530	
" 28	"	{ Vin. colchici, 15 m. } ter die	1210	1014	22.990	0.584	1.63	0.045	0.636	
" 29	"		1813	1011	22.263	0.552	1.59	0.068	0.738	
" 30	"		1814	1012	19.054	0.501	1.46	0.055	0.678	
Dec. 1	"		1645	1013	22.207	0.595	1.64	0.053	0.672	
" 2	"		1870	1012	20.944	0.492	1.51	0.042	0.572	
" 3	"		1450	1015	20.385	0.476	1.40	0.044	0.394	
" 4	"	{ Quinine sulph., 3 gr. } ter die	1900	1012	24.264	0.560	1.70	0.051	0.613	
" 6	"		1680	1013	23.522	0.573	1.54	0.048	0.504	
" 7	"		1245	1016	22.416	0.512	1.46	0.069	0.463	
" 8	"		1175	1016	19.387	0.501	1.53	0.051	0.407	
" 9	Vegetable diet		1465	1016	22.172	0.498	1.77	0.054	0.572	
" 10	"		1530	1020	19.025	0.618	1.99	0.069	0.520	
" 11	"		1975	1014	21.725	0.711	2.66	0.073		
" 12	"		1480	1016	19.240	0.674	2.47	0.063		
" 13	Animal diet		1225	1016	23.275	0.666	2.12	0.061	0.699	
" 14	"		940	1016	23.623	0.458	1.47	0.039		
" 15	"		930	1018	24.180	0.557	2.35	0.054		
" 16	"		875	1020	23.625	0.543	1.88	0.058	0.609	
" 17	Animal diet + tea		1134	1017	25.484	0.688	2.25	0.055	0.941	Temp. 103°.
" 18	"		1010	1018	23.735	0.649	1.11	0.057	0.709	

deposition of biurate, should be experimentally induced by one of the alloxur bases, and this suggests that one or more of them may be a factor in the evolution of gout. As negative evidence of such a causative relation there is the further fact that uric acid has not been shown by experiment to produce any such symptoms—a statement of special significance as regards the circulatory disturbance. The extreme insolubility of uric acid also points to the possibility that, with an advancing knowledge of the pathology of gout, it may be relegated to a secondary position in the causation of that disease. Apart from xanthin, the amount of alloxur bases appearing in the urine is so exceedingly small that their separate estimation is a matter of great difficulty. Supposing, therefore, the excretion of adenin were diminished or increased, such a variation would only in a slight degree alter the total quantity of the bases; hence the fact of the bases varying within normal limits in proportion to the acid does not exclude the possibility of adenin being retained in the system, and thereby determining the deposition of biurate in the tissues. It is to be regretted that this line of research has not been extended; but pure adenin is almost impossible to obtain at present.

Regarding the supposed nuclear origin of uric acid which links it with the output of phosphorus pentoxide, its proportionate relation to that substance was not so consistently maintained as was anticipated from previous observation. On several occasions during the first fortnight through a misunderstanding there were slight but, as regards phosphates, possibly effective variations in the fixed diet. It is of course necessary in order to observe the relation in question that the diet should remain absolutely unchanged both in quantity and quality. Dr. Chalmers Watson, in a paper of much interest, has thrown doubt on the parallel variations in the excretion of these two products as tentatively advanced by me in a former communication. Possibly he overlooked the statement that in gouty cases retention is a perturbing factor.

Another disturbing factor to which, however, no reference was made in my paper is excessive excretion of uric acid such as follows the exhibition of eliminative drugs. An example of this will be found in the tables. As regards his case it was not stated that the patient's food was weighed, and further potassium iodide was being administered during the major part of the investigation. It has occurred to me that the discrepancy may be dependent upon either or both of these circumstances. For the estimation of uric acid Dr. Watson used a modification of Salkowski's silver method. Silver having a greater affinity for iodine than for uric acid, it follows that unless sufficient silver were added to precipitate both the iodine and the uric acid a part of the latter would remain in solution. In Table II an average has been taken of the estimated constituents of the urine, the last three days average under ordinary conditions being placed first for comparison.

TABLE II.

	Averages, in Grams.				
	Urea.	Uric Acid.	P ₂ O ₅ .	Alloxur Bases.	Ammonia.
Fixed diet (3 observations)	20.839	0.492	1.48	0.052	0.567
Sodium salicylate (3 ")	22.165	0.521	1.61	0.069	0.485
Guaiacum (3 ")	18.282	0.716	1.32	0.052	0.784
Potassium iodide (3 ")	22.429	0.574	1.48	0.056	0.653
Colchicum (4 ")	21.853	0.558	1.56	0.050	0.681
Quinine (2 ")	23.892	0.566	1.62	0.049	0.558
Vegetable diet (4 ")	20.505	0.625	2.24	0.064	0.546
Animal diet (4 ")	23.675	0.556	2.00	0.053	0.654
Animal diet + tea (1 observation).	25.484	0.688	2.25	0.055	0.941

It is unnecessary to trace in detail the effect of the drugs given, as this is apparent in the tables. Contrary to expectation, after sodium salicylate there was only a small increase

in uric acid, with a slight augmentation of the alloxur bases relative to the acid. Under guaiacum, on the other hand, while the urea fell somewhat, the uric acid was markedly increased; but neither the phosphorus pentoxide nor the bases showed a corresponding increase, thereby denoting that this drug probably acts not by increasing the production of uric acid, but by eliminating a part of that stored in the blood. The bearing of this fact on the treatment of chronic gout will be appreciated. It is also noticeable that the increased excretion of uric acid was maintained for some time after cessation of the drug, the patient's condition being at the same time ameliorated. It is satisfactory to note that the experimental evidence adduced confirms the opinion, based on empirical knowledge, expressed by Sir Alfred Garrod that guaiacum was a powerful prophylactic agent in gout, this opinion being subsequently corroborated by Dr. Luff.

The raised excretion of uric acid with potassium iodide is probably attributable to the maintained effect of guaiacum. The value of potassium iodide in chronic gout is founded rather on its apparent power of retarding cardio-vascular and renal changes, and reducing albumen in the urine. Under colchicum a slight advance in the uric acid occurred. That it has an invariable effect on the excretion of uric acid is extremely doubtful. The result with quinine on the excretion of uric acid is contrary to the diminution usually observed. This again may be accounted for by the continued improvement in the patient's condition.

The results obtained with the experimental diets are not in agreement with the generally accepted view upon which the dietetic treatment of gout is frequently based. There is matter for reflection in the fact that a diet consisting largely of leguminous principles should so markedly increase the uric acid, the phosphorus pentoxide, and alloxur bases.

On the second day after tea was added to the animal diet the patient developed a temperature due to a chill which terminated the observations, so that no reliable inferences can be drawn from the record with regard to the influence of tea upon the urinary constituents estimated.

THE GELATINOUS FORM OF SODIUM BIURATE AND ITS BEARING ON THE TREATMENT OF GOUT.*

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I do not propose in this paper to touch upon the debatable questions of the seat or seats of formation of uric acid, or of the compounds from which that body may be derived. I believe, however, that it is a practically indisputable fact that the deposition of a salt of uric acid—namely, sodium biurate—is intimately related to the gouty attack, and I propose to briefly bring forward to-night the results of some experiments which I think throw some light on the therapeutics of gout.

I strongly share the view of the late Sir William Roberts that uric acid, when first introduced into the blood, exists solely therein as the sodium quadriurate. This substance is, in the dissolved state, a very unstable body, and soon changes into the sodium biurate, which first assumes the gelatinous and soluble form. This gelatinous modification, if not eliminated in the urine, is converted either slowly or rapidly, according to various conditions, into the crystalline and almost insoluble variety, which is then precipitated, and, by its deposition in various structures, causes the gouty paroxysm. It is obvious that if by any means the conversion of the soluble gelatinous biurate into the insoluble crystalline form can be delayed, then the advent of the gouty paroxysm is also delayed, and if, during this period of delay, the elimination of the soluble gelatinous biurate is promoted, then the gouty paroxysm may either be considerably diminished in severity or may even be averted altogether.

I have for some time been studying the physical and chemical properties of this gelatinous form of the biurate, and especially the effects exerted by certain drugs on its conversion into the crystalline form. The drugs the influence

of which on the gelatinous biurate I have experimentally investigated are sodium bicarbonate, sodium phosphate, potassium bicarbonate, potassium citrate, lithium carbonate, lithium citrate, piperazine, and lysidine. In a paper which I communicated to the last meeting of the British Medical Association,¹ I showed that by increasing the alkalinity of blood serum with sodium bicarbonate the conversion of the gelatinous biurate into the crystalline form is accelerated in time and increased in quantity, whereas when the alkalinity of the serum is increased by the addition of potassium bicarbonate the conversion of the gelatinous biurate into the crystalline form is delayed as regards time, and is considerably diminished as regards quantity. I have now carried out a similar series of experiments with the other drugs previously mentioned.

Briefly stated, the results show: (1) That sodium salts considerably accelerate the conversion of the gelatinous biurate into the crystalline variety, and that their employment in the treatment of gout is apparently not desirable; (2) that potassium salts delay the conversion of the gelatinous biurate into the crystalline form, and also that when the conversion is once started it is slowed by the presence of these salts; (3) that lithium salts, although they do not delay the initial conversion of the gelatinous biurate, yet when the conversion is once started it is slowed by the presence of these salts, and especially by the lithium carbonate; (4) that piperazine does not delay the initial conversion of the gelatinous biurate, and but slightly slows the conversion when once started; and (5) that lysidine, although it delays the conversion of the gelatinous biurate into the crystalline form, yet when the conversion is once started it has practically no effect in slowing it. From the results of these experiments it appears that for the special purpose referred to in the treatment of gout the potassium salts are the most useful, that the lithium salts rank next, and that piperazine and lysidine are not nearly so useful. I may mention that these results are entirely in accord with my clinical experience.

I do not for one moment contend that the beneficial action of the salts of the alkali metals in the treatment of gout is to be solely gauged either by their solvent action on deposits of sodium biurate, or by their inhibitory action on the conversion of the gelatinous biurate into the crystalline form. Undoubtedly many of them are extremely useful in the gouty state by their stimulating effect upon metabolism, by their remedial action upon the gastric and hepatic functions, by their diuretic action, and by their diminishing the acidity of the urine. I should like to remark here that the purport of a paper published by me in the *Lancet* of June 11th, 1898, has been somewhat misunderstood. In that paper I showed by experimental evidence that potassium, sodium, and lithium salts, and piperazine and lysidine exercised no appreciable solvent action on gouty deposits. I did not, however, question—still less deny—the utility of many of these drugs in the therapeutics of gout, for I am constantly employing many of them in the treatment of various phases of that disease; but I wished to point out that the oft-repeated statement that most of these drugs are useful for their great solvent action on gouty deposits is a loose and erroneous statement which it would be wiser in future to avoid.

Another important point demonstrated by these experiments is that the higher the alkalinity of the blood from the presence of sodium bicarbonate, the more rapid and the more complete is the conversion of the soluble gelatinous biurate into the comparatively insoluble and crystalline form. This point is of great interest, since I believe that the alkalinity of the blood of gouty patients is always higher than the normal alkalinity of blood. I know that this view is opposed to the prevailing view that gout is associated with what is called an "acid dyscrasia"—whatever that may mean—and that consequently the alkalinity of the blood of gouty subjects is below the normal. This view, however, so far as I can ascertain, is a pure assumption, and has apparently never been based upon any actual determinations of the alkalinity of the blood of gouty individuals. It received its first shock five years ago, when Klemperer showed by actual determinations of the blood of gouty subjects that the alkalinity was not below that of healthy blood. I have since made a number of determinations of the alkalinity of the blood of healthy and gouty individuals, with the result that I have so far found in

* Read before the Medical Society of London.