URIC ACID AND GOUT: SOME POINTS IN THE PHYSIOLOGY OF URIC ACID.

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It has long been known that the part which uric acid plays in disease is highly important, but its exact nature still lacks definition. The relationship which it bears to the various manifestations of acute and chronic gout and other disordered states of metabolism will not be definitely known until we have a fuller knowledge of the part played by it under normal conditions, and of its seat of formation in health. A good deal has of late years been written on this subject, both by physiologists and physicians, but a marked diversity of opinion still exists regarding this fundamental point. As I have for the past year been engaged in an investigation on the seat of formation of uric acid in health, and have obtained results at variance with views lately expressed by some medical writers on this subject, I propose to give a short account of my work and the conclusions derived from it. The investigation consisted in the examination of the blood of birds and that of a snake; also the viscera of birds, snakes, and various mammals.

The main by-product of nitrogenous metabolism in man and mammals is urea, in birds and reptiles uric acid; but in the mammal a small quantity of uric acid is also excreted, the daily amount in man being half a gram. If we bear in mind that it is by no means easy to prepare urea from the blood of mammals, even although the amount of that substance excreted daily is about sixty times greater than that of uric acid, it is not surprising that great difficulty has been experienced in recognising the presence of the latter in the blood of a mammal. For a fuller investigation of the subject we must have recourse to an examination of the blood and viscera of birds and reptiles whose main nitrogenous by-product is uric acid. Here again, however, we must bear in mind that even although uric acid be present in relatively large amount in the urinary excretion, it would not be surprising if the amount present in the blood at a single examination were very small. This is in accordance with the results of previous observers.

SEAT OF FORMATION OF URIC ACID.

Before passing to a description of investigations it may be advisable to give a short summary of the main views entertained regarding the seat of formation of the substance under discussion. The organs which have been so regarded are: (1) The liver; (2) the kidneys; (3) the spleen, thymus, and other nuclear-holding tissues.

Although it has been customary to speak of the mode of formation of uric acid in birds as distinct from that in mammals, it is not unlikely that there are seats of formation common to both. The largest amount of fruitful work on the subject has been done in the case of birds, owing to the fact that, as more is excreted by them, one expects also a greater formation, although this conclusion is not a necessary one.

The Liver as the Seat of Formation.—With regard to the views held in support of the theory that the liver is the principal seat of production, the work on which these views were based has been carried out mainly on birds. Meissner¹ found a larger quantity of uric acid in the liver than in any other organ, and concluded that this organ was the principal seat of its formation. Minkowski² corroborated this conclusion. He found on removing the liver from the circulation of geese, that amido-acids were no longer transformed into uric acid, and the nitrogen appeared in the urine mainly in the form of salts of ammonia. He considered that this splitting off of ammonia always occurred as a precursor of the formation of uric acid. Schroeder,³ in an important series of observations, showed that in birds and snakes uric acid could be formed outside the kidney. He and other observers, notably Knierien, Cech, Salkowski, and Jaffé, showed that amido-acids, urea, and carbonate of ammonia were transformed in the fowl into uric acid. Schroeder also estimated the amount of the acid present in the different organs, and, finding that the liver contained the largest amount, agreed with Meissner that it is the organ mainly

concerned in its formation. Scherer, Cloetta, Grüber, and v. Gorup also recognised its presence in the liver and other organs. The methods employed in their researches were, however, not free from fallacy.

The Kidney as the Possible Seat of Formation.—Zalesky, in 1866, performed certain experiments on hens, geese, and serpents. He first tried the ureters of hens and geese, and found that uric acid was deposited in the tissues. He then removed the kidneys from serpents, and, finding that no uric acid was deposited, concluded that the kidney was the seat of formation. This view, however, was soon contradicted by, among others, Meissner and Chrzonszczewsky. Kolisch,⁴ among the more recent workers, also regards the kidneys as the most important of the uric acid-forming organs. He considers that nuclein bases are there transformed into uric acid. No evidence of any weight has been brought forward in support of this view, and his statement that in cases of parenchymatous nephritis the nuclein bases are increased whilst the uric acid is diminished has been shown by numerous observers to be erroneous. Abeles⁵ was unable to obtain any production of uric acid by an artificial circulation of its probable precursors through the kidneys. Sir A. Garrod⁶ supports the view that uric acid is mainly produced in the kidney because he failed to find uric acid in the blood of birds. Dr. Luff⁷ also expresses the opinion that the kidney is the sole seat of formation of uric acid in health. His opinion, like that of Garrod, is based mainly on the assumption that uric acid is normally absent from the blood of birds and mammals.

The Spleen and other Tissues as Probable Seats of Formation.—Numerous observers—notably Scherer, Cloetta, Messner, Grüber, and v. Gorup—have shown that uric acid is present in the lungs, brain, pancreas, blood, and various pathological fluids. In all these cases the identity of the substance was established by its precipitation out of hydrochloric acid solution and the application of the murexide test to the deposit. It was not, however, until Horbaczewski⁸ showed that the acid could be formed from nuclein-holding tissues, that great attention was directed to other parts as the probable seat of its formation. He showed that uric acid could be formed by allowing blood to digest with splenic tissue under conditions admitting of free oxidation. Similar results were obtained by digesting nuclein and nucleic acid under the same conditions. The work which led up to Horbaczewski's experiments was that of Kossel and his pupils, who showed the intimate connection between the nucleins and those bases that possess the same alloxan nucleus as uric acid—namely, the alloxur or nuclein bases. In view of Horbaczewski's experiments, it is very surprising that Stadthagen⁹ failed to find uric acid either in the normal or leucocythæmic spleen; although in both cases, but especially in the latter, a very large amount of alloxur bases were present. Bockendahl and Landwehr corroborated Stadthagen's statement as to the absence of uric acid from the spleen in leucocythæmia. Scherer¹¹ is in fact the only investigator who has obtained it from this organ in that disease. I may here add, although I shall refer to this in a later paper, that I also have found uric acid in the leucocythæmic spleen, and that in appreciable quantity.

From the foregoing it is evident that our knowledge of the true seat of formation of uric acid is as yet very uncertain. There is still a marked difference of opinion on such a fundamental point as the existence of uric acid even in the blood of birds and reptiles, while of course still greater doubt exists as to its presence in mammalian blood and tissues. That being so, it seemed advisable to repeat some of the observations previously made, using the more modern methods of examination. I have accordingly examined the blood of birds, a snake, and mammals, and thereafter the viscera of these animals in the manner described.

EXAMINATION OF THE BLOOD.

The defibrinated blood was obtained fresh and examined as follows: The albumen was first removed by diluting the blood with seven to eight times its volume of water, heating to boiling point, acidifying with a few drops of acetic acid, filtering, and finally extracting the coagulum with boiling water. A clear filtrate was obtained and evaporated to dryness, at first on the open flame, and then on the water bath. The residue was then extracted with a large quantity of boiling water and filtered. The phosphates in the solution

were precipitated by ammonia and magnesia mixture, and removed by filtration. Silver nitrate solution (30 grams to a litre) was then added until no more precipitate appeared, care being taken that the mixture was strongly ammoniacal. This was then set aside in a dark place for an hour or more, and thereafter filtered by means of a suction pump, the precipitate being washed free from chlorine by the use of weak ammoniacal solution. The magnesium silver urate was then decomposed by passing through it a stream of H_2S in acid solution. The fluid was now brought to boiling point and filtered. The clear filtrate thus obtained was evaporated down to about 5 c.cm., at first on the open flame and finally on the water bath. A few drops of hydrochloric acid were then added, and the fluid set aside for twenty-four hours to allow the uric acid to crystallise out. The following tests were then applied for the determination, qualitatively and quantitatively, of the acid.

1. The deposit was submitted to microscopic examination.
2. The murexide test was applied, after purification.
3. The sediment, when weighable, was collected on a filter paper previously dried and weighed, and the total weight ascertained.

4. The nitrogen in the deposit was estimated by Kjeldahl's method and expressed in terms of uric acid. This served as a valuable check on the weight previously recorded, and indicated whether the substance in question was practically pure uric acid or not.

A point of importance has to be noted in the above application of the murexide test. If the sediment has not previously been washed chlorine free this test is fallacious, as it is so easily confused with Weidel's xanthin reaction. In every case, therefore, the deposit was washed chlorine free and the amount of wash water measured, 10 c.cm. being estimated as equivalent to 0.5 mg. uric acid.

I here tabulate the results obtained from the examination of the blood of birds and other animals.

Birds.

			Total Uric Acid.	Percentage.
Obs. 1	Duck	1,750 c.cm.	0.0352 gram.	01' 0.0020 gram.
" 2	Goose	1,650 "	0.0428 "	01' 0.0025 "
" 3	Turkey	1,500 "	0.0328 "	01' 0.0021 "

Note.—50 c.cm. of duck's blood were also examined and gave a positive result as regards the presence of uric acid. The sediment obtained was exceedingly scanty, but showed microscopically a few lozenge-shaped and rhombic crystals, which gave a distinct murexide reaction. No further examination was available.

Snake.

4. Blood and Heart.—On account of the very small quantity of blood present in the snake, it was considered advisable to remove the heart and large vessels with the contained blood and examine as a whole. A very fine deposit was obtained, which gave a distinct murexide reaction. The amount, calculated from the nitrogen obtained was 0.0031 gram, including 0.6 mg. from the wash water used.

Mammals.

5.	Lamb	1,100 c.cm.	A distinct though delicate murexide reaction was obtained.
6.	Dog	500 "	No trace of uric acid was obtained from this examination.

EXAMINATION OF THE ORGANS OF BIRDS AND MAMMALS.

The liver, kidney, and spleen of various birds and other animals were then examined. The details of the method of examination are as follows: Each organ was finely minced and weighed, and a small quantity taken for the estimation of the water percentage. The uric acid was extracted by the addition of a large quantity of boiling water, the whole being brought to boiling point and a few drops of acetic acid added to ensure complete coagulation of the albumen. The contents were filtered, the filtrate being then evaporated down almost to dryness, at first on the open flame, and later on the water bath. The residue was extracted with a large quantity of boiling water and filtered. Thereafter the procedure was as already described for the examination of the blood. The following is a note of the observations made, the

weights recorded representing the amount present in the organs, water free.

Birds.

				Total H ₂ U.	Percentage.
Obs. 1	Turkey	Liver Kidney Spleen	Grams. 34.0 6.7 0.6	Gram. 0.0230 0.0122 None	Gram. or 0.0676
" 2	Turkey	Liver Kidney Spleen	43.0 ¹ 3.5 0.6	0.0702 0.0026 None	or 0.1628
" 3	Duck	Liver Kidney	28.0 2.5	0.0180 0.0025	0.0642
" 4	Hen	Liver	16.5	0.0101	0.0612
" 5	Hen	Liver Spleen	12.8 1.1	0.0196 None	— —

¹ The 43 grams above stated include 9 grams of hen's liver received along with the turkey's viscera.

Snake.

				Total H ₂ U.	Percentage.
Obs. 6	Snake	Liver Kidney Spleen Lung Intestine with its contents	Grams. 8.5 2.8 — — —	Gram. 0.0066 0.0031 None " 0.0375	Gram. — — — — —

Note.—At one stage of the examination of the intestine rather more than half the total fluid was inadvertently lost. The large quantity of uric acid present in the remainder was striking.

Mammals.

				Total H ₂ U.	Percentage.
			Grams.	Gram.	Gram.
Obs. 7	Sheep	Liver	173.0	0.0227	or 0.0131
		Kidneys	23.0	None	—
		Spleen	14.0	Mere traces	—
" 8	Sheep	Liver	206.0	0.0209	or 0.0101
		Kidneys	12.0	None	—
" 9	Calf	Liver	656.0	0.0467	0.0071
		Kidneys	65.0	None	—
		Spleen	51.0	0.0110	0.0215
" 10	Calf	Kidneys	78.0	0.0045	0.0057
" 11 ¹	Dog	Spleen	72.0	0.0115	0.0159
		—	—	—	—
" 12	Rabbit	Kidneys	3.7	None	—

¹ The liver, kidneys, spleen were examined, and revealed no trace of uric acid.

The results of these investigations may now be summarised:

BIRDS.—Uric acid was found in the blood, liver, and kidneys. The absolute amount was greater in the liver than in the kidney.

SNAKE.—Uric acid was found in the heart which contained a relatively large amount of blood, liver, kidneys, and intestinal contents, the absolute amount being greater in the liver than in the kidney. A relatively large amount was found in the intestinal contents.

MAMMALS.—A. *Dog and Rabbit.*—In the dog the blood, liver, kidneys, and spleen contained no uric acid. A similar result was found with the kidneys of a rabbit.

B. *Sheep and Calf.*—Mere traces of uric acid were found in the blood of a lamb.

With regard to the viscera of these animals three points have to be noted:

1. The absolute amount in the liver was greater than that in the other organs.

2. The kidneys contained less than the spleen, both as regards absolute amount and percentage.

3. The spleen seemed to contain a higher percentage than the other two organs.

CONCLUSIONS.

It is not my intention to draw from these results any conclusions as to the seat of formation of uric acid. I propose to continue the investigation, and meanwhile avoid making any

theoretical deductions from the results already obtained. I have satisfied myself, however, as to the following two points:

1. That uric acid is present in the blood of birds.
2. That as far as my observations go, there is no evidence in support of the view advanced by Garrod and Luff that the kidney is the main seat of formation of uric acid.

In conclusion I must in the first place express my indebtedness to Professor Rutherford for allowing the research to be carried out in his laboratory, and for valuable suggestions in connection with it. I have further to express my special indebtedness to his assistant, Dr. T. H. Milroy, for much valuable assistance throughout the whole investigation. I am also indebted to Dr. Selby, Wigtonshire, for the large quantities of blood examined, and to Professor Mettam, Veterinary College, for kindly giving me the viscera of the snake. The expenses incurred in the investigation were covered by a grant received from the Moray Research Fund of this University.

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ON BELLADONNA IN THE TREATMENT OF BRONCHO-PNEUMONIA IN CHILDREN.*

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I WILL preface what I have to say by stating that I hold to the prevalent belief that there is an essential difference between croupous pneumonia and broncho-pneumonia in children. Cases, it is true, are not uncommon in which, judging from the physical signs alone, there may be extreme difficulty at the outset in determining to which class, croupous or catarrhal, they rightly belong. This difficulty doubtless arises from the fact that a well-defined patch of croupous pneumonia in young children is apt to be accompanied by small patches of collapse, and subsequent consolidation, in the immediately surrounding pulmonary tissues. Here the signs of broncho-pneumonia may complicate, or follow upon, those belonging to a case essentially of the croupous form at the outset of the illness. The course or termination of the attack, in the vast majority of instances, generally helps to clear up any hesitation in deciding as to the variety to which they mainly belong. Apart from such doubtful, or rather mixed, cases, however, in which there may be temporary room for doubt in classification, there is a vast majority of typical cases in each section, in which the initial symptoms, the course of the complaint, the parts of the lungs affected, the physical signs, the termination, and sequelæ are sufficiently distinct to differentiate sharply between them.

For these reasons I am not inclined to agree with some views recently put forward as to the identity of the two complaints in children. These views, too, are mainly founded on bacteriological grounds, and, in my opinion, the bacteriology of either form is not as yet sufficiently established to upset the prevalent belief in the distinctive character of the two complaints. As furnishing one criterion between them, I might appeal to the totally differing mortalities in the two forms of the complaint. At the Shadwell Children's Hospital, even with weakly East End children, a mortality of 10 per cent. would be above the mark in cases diagnosed as croupous pneumonia. In contrast with this, in cases diagnosed as broncho-pneumonia the mortality has generally, in children under the age of 2 years at least, ranged from 60 to 80 per cent. This increased mortality, if it establishes nothing else, sufficiently demonstrates the greater gravity of cases diagnosed by several observers as broncho-pneumonia over those

diagnosed by the same set of observers as belonging to the croupous form.

There is a wide difference, too, in the treatment of the two complaints. In the majority of cases of croupous pneumonia all that is needed is careful nursing and feeding, any active interference on the part of the physician being seldom called for. On the other hand, in the majority of cases of catarrhal pneumonia every remedy that experience or ingenuity could suggest has been invoked. Foremost among these have been such measures as steam tents, inhalations of oxygen heated over steam coils or given cold, injections of strychnine, alcohol in large doses and other drug stimulants, dry cupping, leeching, and emetics. With such active treatment, doubtless many a life has been saved. But in spite of all these, coupled with the most devoted attention of the nursing and resident medical staffs, our mortality in broncho-pneumonia remained appallingly high. Any remedy that would serve to diminish this mortality deserves consideration. Such a remedy we think at present we have found at Shadwell, in somewhat large doses of belladonna.

It is known, although I believe not as widely or generally as its importance deserves, that cases of that very fatal sequela of diphtheria—paralysis of the diaphragm—can often be cured by pushing belladonna or atropine to their full physiological limits. Since using belladonna or atropine in full doses a large proportion of such cases have recovered. For the knowledge of this property of belladonna I am indebted to several members of the staff of the Great Ormond Street Hospital. From no one, however, could I gain any satisfactory explanation as to how the drug acted. The only one afforded me was that belladonna in some way stimulated the respiratory centre, and so the effect of the diaphragmatic palsy was counteracted by over-exertion on the part of the other respiratory muscles.

To me, I confess, such an explanation was far from a convincing one. I could not conceive any drug acting continuously as a stimulant on the respiratory centre for the three or four days during which the greater stress of the palsy lasts, without there being corresponding times when this hyper-stimulation would be replaced by depression and its attendant evils. Whilst, then, accepting the fact of the beneficial action of belladonna in palsy of the diaphragm, I was compelled to leave any explanation of its mode of action to the unsatisfactory region of the empirical.

About a year ago, however, renewed attention was called, I think by Dr. Ringer, to the marked effect atropine had in limiting or diminishing secretion into the bronchial tubes and pulmonary tissues. It was pointed out that numerous patients recovered from the immediate effects of an operation, merely to die in three or four days choked by the undue effusion into the bronchial tubes, induced by the action of the ether or other anæsthetic used at the time of operation. For the prevention of this water-logging of the lungs from the anæsthetic it was proposed that patients for several days after operation should be treated with atropine or belladonna. Such a practice is, I believe, carried out in a routine manner in at least one large London hospital.

This view of the action of belladonna seemed to me to furnish the explanation wanted of its beneficial action in diphtherial paralysis of the diaphragm. Belladonna, I would suggest, has no direct influence on the course of such paralysis, it merely prevents or diminishes the secondary pulmonary effects consequent on it, and so staves off an impending asphyxia. In this view of its action, too, the routine treatment of diphtherial paralysis with belladonna, practised by some eminent specialists, and doubtless founded on experience gained from cases of paralysis of the diaphragm, to my mind is illogical and likely to be futile, unless the last named grave complication is present or threatening.

For reasons based on the above conclusions I determined to give belladonna a trial in the treatment of broncho-pneumonia in children. If the drug possessed the powers ascribed to it, then it seemed to me that in broncho-pneumonia, with its free secretion into the bronchial tubes and pulmonary tissues, just such conditions obtained as the drug would control and counteract. So far it has more than answered all that I could have hoped for. With it as the sole drug administered there has been in my cases no need for steam tents, oxygen inhala-

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