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E. VII

URIC ACID

AS

A FACTOR IN THE CAUSATION OF DISEASE

A CONTRIBUTION TO THE

PATHOLOGY OF HIGH ARTERIAL TENSION, HEADACHE, EPILEPSY, MENTAL DEPRESSION, GOUT, RHEUMATISM, DIABETES, BRIGHT'S DISEASE,

AND OTHER DISORDERS

BY

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PHYSICIAN TO THE METROPOLITAN HOSPITAL, AND THE ROYAL HOSPITAL FOR CHILDREN AND WOMEN; LATE CASUALTY PHYSICIAN TO ST. BARTHOLOMEW'S HOSPITAL.

Second Edition

WITH THIRTY-SIX ILLUSTRATIONS

LONDON

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PREFACE TO THE SECOND EDITION.

SHORT as is the interval since the appearance of the first edition the subject has made great strides, and where it has not advanced old positions have been very greatly strengthened and consolidated.

The chapter list shows new matter on uric acid and metabolism, fatigue, asthma and bronchitis, dyspepsia and gout of the intestines, Raynaud's disease, anæmia, and instruments and methods, this last being written in response to very numerous enquiries on these subjects from readers of the first edition. Then much of the old work has required revision in reference to new discoveries, so that this is a new book and not a mere re-issue of the first edition.

In addition to those friends whose names I mentioned in the first edition, whom I now desire to thank once more, I must return my grateful thanks to a large number of fellow-sufferers and fellow-workers for the interest they have taken in the investigation, and for the help they have given me in the shape of notes of their own and other cases. Some of these I have mentioned in the text, but others which I have been unable to mention have yet been of great help in directing my attention to important points. I hope that such fellow-workers may continue to increase, and that they will eventually carry the research far beyond anything that it may be in my power to accomplish, as I am more than ever convinced that it will repay all their labours.

ALEXANDER HAIG.

7, *Brook Street,*
Grosvenor Square, W.
April, 1894.

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PREFACE.

THIS is practically a *résumé* of the facts and arguments in some twenty-five papers, on the subjects which form the headings of the chapters, which have appeared in various journals, transactions and reports from the year 1884 to the present time, together with such alterations and additions as further experience has suggested.

As my investigations tend to show that the functional and organic disorders of which I speak are in many cases entirely due to an excess of uric acid in the body and blood, this is practically a work on the causation of disease by uric acid, of the process by which it comes to be present in excess in the body, and of the means of preventing such excess.

I nevertheless regard the investigation at which I have been working during these years as only in its very first stages, and this volume as a mere preliminary communication, and one which was only undertaken because I felt that papers thus scattered about in various journals did not do the subject justice; and it is certainly not with any feeling that the matter is ripe for final judgment that I now put it forward.

Considerations of space have compelled me to give in mere outline much of the results of my work during the last six years, but any portions which the future may show to be of value can easily be recorded at greater length. It would also have been almost impossible to carry through the thread of my argument if greater details had been given here.

My most hearty thanks are due to Dr. Lauder Brunton for much kind assistance, advice, and encouragement, and my readers will doubtless see that the investigation has not been by any means devoid of difficulties and doubts, though some of these now seem to have been happily surmounted.

I am also under considerable obligation to Sir Dyce Duckworth for allowing me to investigate certain interesting cases and for much kindly notice and instructive criticism of my researches in his work on "Gout;" also to Dr. Norman Moore and Dr. Ormerod for permission to work in the departments under their charge at St. Bartholomew's Hospital, and to my colleague, Dr. H. H. Tooth, for permission to quote some cases, and for much assistance in studying epilepsy from my point of view.

I have also to thank Mr. J. E. Saul for kind help in several places with regard to points in chemistry where I should otherwise have been at fault, and to many others who, as appears in the text, have helped me by permission to study their cases, copy their notes, or profit by their experiences, I must here also return my grateful thanks.

ALEXANDER HAIG.

7, *Brook Street,*
Grosvenor Square, W.
February, 1892.

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URIC ACID

AS A

FACTOR IN THE CAUSATION OF DISEASE.

CHAPTER I.

History.

It is now eleven years since I began the research of which I propose to give an account in the following pages.

It seemed to me then a small and simple matter to investigate the causation and treatment of the headache from which I suffered; but gradually through these years the horizon has expanded, and I now see that if even a half of my deductions are eventually substantiated, a very large portion of the field of medicine will be modified thereby.

It will easily be understood, then, that I am not here attempting any complete and finished picture; but as it has seemed to me that my results being published as yet in several journals and at various times, the subject has never presented to those who may have read my more or less isolated papers the same cohesion and strength which a survey of the whole field, even though necessarily incomplete, may afford, I shall endeavour to remedy this defect by giving as shortly as possible a consecutive statement of the main points.

Having been all my life a sufferer from migraine it was in the autumn of 1882 that in despair of obtaining any complete relief from drugs, and not without some fear that I was really suffering from organic disease, I gave up all butcher meat and replaced it by milk and fish.

I had previously tried a great variety of alterations in diet, including an increased allowance of meat and various alterations in quantity and quality of less important constituents, such as sugar, tea, coffee, and tobacco, without any noticeable result. But on the non-meat diet a change was at once apparent; my headaches diminished both in frequency and severity, and from an average of one in a week they fell steadily, as the diet was persevered in, down to one in a month, one in three, six, eight, or twelve months, and eventually eighteen months elapsed without an attack of notable severity.

Since that I have never gone back to butcher meat, and I never intend to, because by avoiding it I obtain what is practically immunity from a disorder which, at one time, bid fair to cripple me and prevent completely all mental and sedentary work; not that the headache was confined to periods of sedentary work, for I have often had to give up portions of a day's shooting because my head was too bad to stand the noise and concussion of firing, and yet this was in the open air of the country, and when a book had probably not been opened for weeks, and under conditions which were infinitely more favourable to health than those in which I now exist and have immunity.

But if I at any time forget my lesson of the past and presume on my apparent security from attack, if I dine with two or three friends in the same week, and especially if I take both meat and wine, of the action of which I shall speak presently, I am practically certain to have a more or less severe headache in two or three days' time; though, as will appear further on, I can generally prevent the intense pain from which I used to suffer in former days.

Having arrived, then, at the conclusion that leaving off butcher meat had practically relieved me of headache, I began to ask why this was so, and at first (*Practitioner*, 1884), I was inclined to attribute it to the formation of some poison possibly of the nature of a ptomaine, in the intestines during the digestion of the butcher meat.

But a further study of the clinical history of migraine brought out such a strong relationship to gout, that (*Practitioner*, 1886) I began to suspect that uric acid might be the poison of which I was in search, and I therefore proceeded to estimate the excretion of uric acid and urea.

At first I estimated only the excretion of twenty-four hours, and as many of my headaches lasted only a portion of a day, I got indefinite or contradictory results; but when I separated the urine excreted during the headache from that both before and after it, a definite and distinct relation between the headache and the excretion of uric acid at once became apparent—a relation which I have since found both in myself and others, in very numerous instances, quite sufficient to remove the result out of the chapter of accidental coincidences. But the headache in question, as described by Liveing and others, has other important concomitant symptoms—as slow high tension pulse, cold surface and extremities, mental depression, and disinclination for exertion, mental or bodily, and the urine during the headache is scanty and of high colour and specific gravity.

But once having noticed the relation of this headache to the excretion of uric acid, I soon noticed that each of its concomitant symptoms bore exactly the same relation to uric acid, that when the pulse was slow and of high tension there was always a greater excretion of uric acid than when it presented the opposite character, and the same with the mental depression and scanty urine.

After this a little further experimentation brought out the fact that the excretion of uric acid was completely within my control, and that I could alter it from day to day or hour to hour in either direction at pleasure (*Journal of Physiology*, vol. viii.).

I now soon found out that in altering the uric acid I could alter the symptoms related to it; that when I produced an increased excretion with alkali, I produced the headache, mental depression, cold surface, slow pulse and scanty urine, and that when I stopped the plus excretion with an acid I removed all these symptoms; so that not only had I acquired the power to produce or remove the headache, but I had also the power to relax or contract the arterioles and capillaries to affect the tension of the pulse, the rate of the heart's action, and thus to influence the circulation in the brain, skin, kidneys, and probably the whole body.

Then I also soon noticed that in curing a headache by giving an acid to diminish the excretion of uric acid, I always produced a certain amount of pricking and shooting pain in my joints (generally in those which had been most used on the day in

question), and it naturally occurred to me that the uric acid was held back in these joints and produced the pains. The uric acid which failed to appear in the urine must have gone somewhere. What more natural than to suppose that it had been retained in the joints (where in gout it is found), and that the pricking pains were the evidence of its presence?

Then on turning to Sir A. Garrod, I found that he had described precisely similar joint pains as occurring in gouty subjects immediately after the ingestion of beer or wine, and a very little investigation sufficed to prove that all beers and wines are strongly acid, so that a very simple explanation could be given of the facts.

Since that I have found not only that an attack of gout can be produced by giving acid, but that what I had observed was only a single instance of a general law, and that all substances which increase the solubility of uric acid increase its excretion in the urine, and do good in those joint troubles which are due to its irritating presence; while conversely, all substances which diminish the solubility of uric acid, diminish its excretion in the urine, and also increase those irritations in joints and other fibrous structures which are due to its presence.

On such comparatively simple facts and observations the whole of my writings have been based, and as side issues I have been led to reason on the pathology of epilepsy, in some cases of which I found exactly similar fluctuations in the excretion of uric acid to those met with in migraine, thus explaining a clinical relationship between these two diseases which had long been known and written about—also on the pathology of rheumatism and rheumatoid disease, the causation of Bright's disease, Raynaud's disease, and paroxysmal hæmoglobinuria and anæmia.

But if uric acid affects the arterioles in the way and to the extent which I claim that it does, it will easily be understood that it must influence for good or evil the function, nutrition and structure of every organ and tissue of the body, from the skin outside to the most central fibres of the spinal cord and brain within.

Naturally the subject is not so simple as might appear from this outline, but that will be sufficiently evident when we come to deal with the points in detail, and I shall endeavour as far as possible to conduct my reader through the same course of reason-

ing that I myself followed, so that I may escape the omission of any important points.

Before going on to do this I shall just mention shortly some passages in the writings of Sir A. Garrod, Dr. Liveing and others, which have had important influence in shaping the course of my investigations.

Sir Alfred Garrod says ("Gout and Rheumatic Gout," ed. iii., p. 6): "Galen, who lived about the later half of the second century, was of opinion that gout was caused by some unnatural accumulation of matters in the part affected. These matters were supposed to consist of phlegm, bile, blood, or a mixture of these fluids, and chalk-stones were considered to be formed by their concretion or solidification."

Our knowledge now at the end of the nineteenth century might be expressed in almost the same words if we substitute "uric acid" for "phlegm, bile and blood."

On a previous page Sir A. Garrod says (p. 2, prev. ref.): "It is by no means rare to hear of inflammation of a joint by one practitioner called gout, by another rheumatism, and by a third rheumatic gout," and if it should appear in the following pages that my work tends to show that these more or less distinct clinical conditions may all be due to accumulation of uric acid, I hope this will not be regarded as a step backward but rather as an advance in that, with greater knowledge of the chemical and physical properties of uric acid we are now able to understand how it may produce very different clinical pictures according to the time during which it acts, according to the quantity in which it is present, and according also to the metabolic activity as well as the structure, vascularity and general anatomical arrangement of the tissue on which it acts.

And we may think rather that the discrepancies of opinion which Sir A. Garrod mentions reflect credit on our profession, who failed to detect essential differences where nature had placed none. Further on Sir A. Garrod says (p. 275), "The causes which predispose to gout independently of individual peculiarity are either such as produce an increased formation of uric acid in the system, or lead to its retention in the blood."

And in the Lumleian Lectures (*British Medical Journal*, January, 1883, p. 549), he says, "May it not be the case that when uric acid exists in the blood it is attracted differently by

different organs, and thus the spleen and liver more frequently contain appreciable quantities than other tissues? or, again, may it not be that in some organs as the spleen, the substance of which, if not acid during life rapidly becomes so after death, while the blood remains strongly alkaline the uric acid becomes less soluble and more easily retained."

I shall presently show how I was led by my results, and without any knowledge of Sir A. Garrod's remarks, to believe that excess of uric acid in the blood and body are almost never due to increased formation, but generally to failure of excretion or retention; and that then, having observed that I was always able with alkalies to increase, and with acids to diminish, the excretion, I adopted (*Journal of Physiology*, vol. viii.) Sir A. Garrod's above-quoted suggestion to explain my results, and have continued to use it ever since.

With regard to lead Sir A. Garrod says (p. 243), "It would appear, therefore, that in individuals impregnated with lead the blood becomes loaded with uric acid, not from its increased formation, but from its imperfect excretion."

The results of my researches seem to me to show that the blood never becomes loaded with uric acid except as the result of previous imperfect excretion, and such imperfect excretion or retention is sufficient to account for the largest quantities I have ever seen in the human body, so that there is no need of excessive formation as an explanation. I do not assert that excessive formation never occurs, but only that I have not met with any conclusive proof of its occurrence, while all the phenomena of disease can be completely explained without postulating the excessive formation of a single grain.

Sir W. Roberts says ("Urinary and Renal Diseases," ed. iv., p. 73): "It may be regarded as probable that the defective power of the kidneys to eliminate uric acid in gout arises from a diminished alkalescence of the blood."

From my point of view it has nothing whatever to do with the kidneys; the urates are not in solution in the blood, and are not brought to them; when they have been got into solution by an alkali and come to the kidneys they are excreted fast enough.

But neither Sir A. Garrod nor Sir W. Roberts knew what I found out, that the excretion of uric acid can be made to vary at any time and in any direction—a discovery which not only

enabled me to explain all the symptoms of the uric acid headache, but also showed me the way in which, by the gradual accumulation of small quantities, very large amounts of urate come eventually to be stored or retained in the body without any excessive formation having taken place. It also showed me that the daily physiological fluctuations in the excretion of uric acid are due to the same cause, and depend on the amount of solvent alkali in the circulation, the greatest excretion of the day occurring in what Sir W. Roberts has called the "alkaline tide," and the smallest excretion in the high acidity period of the night.

I would like to add here one word to express my great respect for the magnificent work of Sir A. Garrod, which, founded as it is on experimental research of the most accurate kind, must for a long time to come remain a landmark for all those who work at uric acid.

And if in a few points I have ventured to give other explanations of the facts than those he suggests, or to think that in some few of his results he may have been misled by the working of a less perfect process than that I have used, that has never prevented me from seeing how greatly I am indebted to the careful records of his experimental work, and to his valuable suggestions founded upon it.

To Dr. Liveing's very interesting work on headache I am indebted not only for a knowledge of the relationship of migraine to gout, but also for that of the relationship of migraine to epilepsy and of both to gout, and it was his quotation from Du Bois Reymond and others that led me to look for a uric acid reaction in epilepsy similar to that I had found in migraine.

Since the first edition of this book appeared (1892) I have made two discoveries with regard to the causation of disease by uric acid: first of all I found that uric acid taken by mouth passes into the blood, and that if this fluid is kept in a condition to hold it in solution it will remain in the blood till the kidney has time to pass the whole of it into the urine; so that of 12 grs. taken by mouth some 10 or 11 grs. can be obtained from the urine within three or four days after it has been swallowed. (See *Journal of Physiology*, vol. xv., p. 167.) Now this brings to the front two important points: (1) That the uric acid excreted normally in the urine comes from two sources, (α) the uric acid formed in the body out of nitrogenous food and (β) the uric acid

introduced into the body in meat, meat extracts, soup, &c., all of which contain it in considerable quantity. (2) That in so far as the morbid processes of which I shall speak in the following pages are due to an excess of uric acid in the blood, they can be produced at pleasure simply by taking that substance by mouth, and thus any one who wishes to do so can repeat my experiments and satisfy himself as to their truth.

My second discovery, which was to a large extent a result of the first, was that uric acid when present in excess in the blood affects its quality in an important manner, producing the changes met with in anæmia, paroxysmal hæmoglobinuria and other diseases, and also counteracting the effects of iron and preventing it from building up the blood and curing these diseases.

Thus I found not only that by administering uric acid I could control the value of the blood fraction (hæmoglobin divided by red cells) in myself and others: but that my own blood fraction actually varies from day to day in accordance with the quantity of uric acid passing through it into the urine.

These are facts of which it is hardly as yet possible to gauge the full meaning; but I have little doubt that they will eventually be found to clear up many points in the causation of disease.

CHAPTER II.

Formation and Excretion of Uric Acid.

One of my most early observations on the excretion of uric acid and its relation to a headache showed that while there might be a bad headache one day, with, say, an excretion of 16 grs. of uric acid in the twenty-four hours, there might be an exactly similar excretion on another day without any headache whatever, and viewing only the absolute excretion of uric acid these observations appear to be contradictory and prove nothing.

It was always necessary, however, to view something besides the absolute excretion of uric acid, viz., its relation to urea, and when this was done a difference between these two days at once came out. On the day when 16 grs. were excreted without a headache, the relation of uric acid to urea was 1—33 (one of uric acid to 33 of urea), but on the day when, with a similar absolute excretion of uric acid there was a severe headache, its relation to urea was 1—18 or 1—20.

The uric acid excretion in the uric acid headache is not only absolutely large, but it is greatly in excess of its normal relation to urea. Before going further we may try to determine what is the normal relation of uric acid to urea in excretion, and also if possible in formation.

My researches have extended over a large part of the last eight years, but taking only the figures of the longer periods of my estimation of my own excretion, we get a total of 1,284 days in which 14,353 grs. of uric acid, 404,792 grs. of urea, and 65,386 grs. of acid (reckoned as oxalic acid) were excreted; giving a relation of uric acid to urea of about 1—28, and a relation of acid to urea of 1—6.1.

These figures divided by the number of days give uric acid 11.1 grs., urea 315 grs. and acidity 50.9 grs. per day.

But the total uric acid is increased probably by about 123 grs. swallowed intentionally for experimental purposes, and say some 300 grs. which were stored in the body before the estimation of the excretion began. (Thus I have calculated from the percentage of urate found in the various organs and tissues after death multiplied by the weight of these tissues in the body that a man of 12 stone would probably have 300 grs. in his various organs and tissues. And as this is probably not an over-estimate I have put down 300 grs. as the quantity in my own tissues, but it must be understood that the calculations I am now making are provisional merely and subject to revision as our knowledge becomes more accurate.)

Subtracting the 423 grs. thus accounted for from the total of 14,353 grs. we get 13,930 grs., as representing the excretion of uric acid in the above 1,284 days, apart from the urate which was intentionally introduced, and apart from that which was already present in the body when the experiment began. This gives a daily excretion of 10.8 grs. of uric acid and a relation of uric acid to urea of 1—29.

But the daily excretion equals the daily formation plus the daily introduction of urate ready formed in the food; and though my food is probably much poorer in urate than that of persons on ordinary diet with an ordinary allowance of butcher's meat, soups and meat extracts, still, there seems to be little doubt that my food does contain some uric acid or other members of the xanthin group equivalent to it. Let us say, for the sake of getting even figures, that I introduce with my food 1.8 grs. of uric acid per day, and subtracting this from the 10.8 grs. of daily excretion, we get 9 grs. of uric acid as the actual quantity of the substance daily produced in my body out of nitrogen introduced into it in other forms, the remainder of this nitrogen furnishing about 315 grains of urea. My weight during the course of this investigation has varied but little from 120 lbs., so that urea is about 2.6 grs. per lb., and uric acid actually formed .075 grs. per lb. During this period I have been on a diet of fruit, vegetables, and vegetable products, plus so much milk, fish and eggs as sufficed to keep my urea about this level, but even on this I have introduced, we are supposing, about 1.8 grs. of uric acid per day = .015 gr. per lb. of body weight, or .6 gr. per 100 grs. of urea.

Let us now try and work out the formation and excretion of a man of 150 lbs. from these data. Let us say that he forms 3.5 grs. per lb. of urea = 525 grs. a day, and uric acid in relation of 1—35 = 15 grs. per day. Then he will introduce in his food .6 gr. of uric acid per 100 grs. of urea = 3.1 grs. Therefore, the total uric acid formed and introduced will be 18.1 grs. a day, and if he excretes the whole of this uric acid it will hold the relation to urea of 1—29. But this man with higher urea per lb. will have higher acidity per lb., for acidity rises with urea in about the relation of 1 of acidity (reckoned as oxalic acid) to 6.1 of urea; and with higher acidity of urine he will have diminished alkalinity of blood, and with this, and depending upon it, lessened solubility and excretion of uric acid, that is to say, he will not excrete all the uric acid introduced in his food or formed in his body, but will retain a portion of it in his body. So that while I, in 1,284 days, have probably washed out of my tissues and excreted some 300 grs. of uric acid because my urea and acidity have been low, this man with higher urea and higher acidity may have retained in his tissues in the same period some 300—400 grs.

Such a man, instead of excreting the full 18.1 grs. of uric acid which is formed or introduced into his body each day, will only excrete, say, 17.8—17.9 grs., retaining in his tissues the remaining .2—.3 of a gr., which in the course of years will amount to many hundreds of grs., and the higher the urea and acidity the greater the proportionate retention will be.

I consider, therefore, that every man who eats what is called ordinary diet with butcher's meat twice a day, and does not at the same time take a great deal of exercise (for exercise keeps down the acidity and increases the excretion of uric acid) will, by the time he is 35 or 40, and certainly by the time he is 50, have accumulated 300—400 grs. of uric acid in his tissues, and possibly much more; and about this time, owing to the large amount of uric acid in his body, he will probably be subject to attacks of some form of gout or chronic rheumatism.

If such a man is killed by an accident at this time a quantity of uric acid, more or less equivalent to the above mentioned amounts, will be found in his tissues. If, on the other hand, he dies slowly after several years of wasting disease very much less will be found, for during his wasting there will be a marked fall

of urea and acidity, his blood will become more alkaline and will take up uric acid from his tissues and pass it in excess in his urine. This is the reason we find erosions with but little urate deposit in the joints of patients who have died of wasting disease; before these patients began to waste all the erosions were no doubt full of it.

In most cases of wasting disease the plus excretion of uric acid, and the excess passing through the blood produces symptoms which it is generally easy to recognise, such as slow high tension pulse, and more or less headache and mental depression, and I doubt not, that in the more or less physiological conditions of mere old age, an excess of uric acid in the blood having a similar causation plays an important part.

With regard to the relation of uric acid to urea in excretion, namely, 1—33 or 1—35, other investigators, Messrs. Yvon and Berlioz (*Rev. de Med.*, September, 1888), found as the result of one series of experiments the relation 1—30, and of another series 1—40; while Lecanu (quoted by Sir Dyce Duckworth, "A Treatise on Gout," p. 120) found much the same relation that I have, viz., 1—33.

There is thus a considerable collection of figures tending to show that the normal relation of uric acid to urea in excretion is 1—33 or thereabouts, and I have ventured to suggest that where this has been found over a very long period of time, it may represent something near the real relative formation of these two substances.

As already mentioned (chapter i.) I have adopted the theory of Sir A. Garrod, that the final stage in the formation of uric acid is the production of urate of ammonium in the kidney.[1]

According to this theory a large part of the urate so formed passes at once down the ureter and is excreted; but a small residue lingers in the kidney or the blood circulating in it, and is eventually carried over by the renal vein into the general circulation; when there it is, according to the same authority, attracted differently by different organs, and tends to be rendered

[1] Sir A. Garrod has recently (1893) read a paper before the Royal Society, in which he shows that there is urea in the blood of birds though their urine contains none. He concludes, I believe, that in birds, just as in man, uric acid is formed in the kidney out of urea and other nitrogenous antecedents which come to it in the blood.

less soluble, and so to be held back and accumulate in certain organs, as the liver, spleen, and certain fibrous tissues, especially those of joints, probably because these tissues are less alkaline than the rest of the tissues and fluids of the body.

Now it has long appeared to me that these theories of Sir A. Garrod would enable me to explain completely all my results regarding the excretion of uric acid; not to mention a whole string of disease processes of which, as we shall see presently, they afford an equally simple explanation.

We are now, however, in a position to return to our original question—why there is a headache one day with an excretion of 16 grs. of uric acid, and little or no headache another day, when an identical quantity is excreted.

Starting with the idea that uric acid might be the cause of the headache in question, it appeared to me that the above-mentioned theories of Sir A. Garrod not only favoured this idea, but afforded a very simple and complete explanation of the way in which an excess of uric acid in the blood was brought about.

Taking it that uric acid is never formed in greater relative proportion to urea than 1—33 (1 gr. uric acid for 33 grs. of urea) how comes it that on any given day uric acid can be excreted in the relation to urea of 1—18 or 1—20?

Obviously Sir A. Garrod's theories supply an explanation ready to hand. If 16 grs. of uric acid are excreted to-day, while judging from the urea excreted only 12 grs. of uric acid were formed, then 4 grs. of uric acid must have come from some other source than the formation of this day, *i.e.*, must have been formed on some previous day, when however they were not excreted, but were held back and retained in the body—in the liver, spleen, joints, or fibrous tissues elsewhere.

And the curves which I have shown to illustrate various papers exactly bear this out. In my paper on "Headache" in the *Transactions of the Royal Medico-Chirurgical Society*, I mentioned that the excess of uric acid on the day of headache was almost exactly made up and accounted for by the amount retained, as shown by the curve on the four or five preceding days (*see* fig. 27.).

So that in so far as the headache was due to uric acid it was due to a fluctuation in its excretion, no alteration in formation

having necessarily taken place, and we shall see presently that the action of various drugs exactly bears out this supposition.

When 16 grs. of uric acid were excreted with 528 grs. of urea (*i.e.*, in the natural relation of formation 1—33) there was never any excess of uric acid in the blood, the whole 16 grs. of uric acid were formed that day in the kidney and passed with the urea at once down the ureter, and there was no headache, because there was no excess of uric acid in the blood.

When, however, 16 grs. of uric acid were excreted with only 396 grs. of urea, a relation of 1—24.7, the whole of the uric acid was not formed in the kidney on this day, and some 4 grs. of it must have come from other parts of the body, as the liver, spleen, joints, in which we are supposing it to have been previously retained.

This uric acid, however, would pass through the blood on its way to the kidney, it would be for some hours in excess in the blood, and would give rise to headache and other signs of its presence, and this is, I think, a good and sufficient answer to our question.

In accordance with this reasoning I have always insisted that the relation of uric acid to urea in excretion is of very great importance, as it shows on any given day whether there has or has not been any temporary excess of uric acid in the blood.

It will be noticed that from the figures previously given I have been excreting relatively more uric acid of late years on a vegetarian diet, than I did previously on a more nitrogenous diet, and yet my headaches have been very much less frequent and severe, and a few words are perhaps necessary to explain this.

The headache depends on the absolute quantity of uric acid circulating in the blood. One grain in the blood will not produce it, but three or four grains will. On my old nitrogenous diet the formation of uric acid and urea were both much greater, urea being some 500 grs. per day, as against some 300 now, but it is obvious that a relative excretion of 1—20, on 500 grs., would give 10 grs. of uric acid to pass through the blood, but on 300 grs. only 6 grs. of uric acid would pass through it; hence it comes about that I now have a headache only once in three, six, or nine months, when several causes producing a temporary fluctuation in excretion, happen to act together; but formerly on a more nitrogenous diet I had one every week.

I would here just remind my readers that if one grain of uric acid is held back in the body every day, nearly one ounce could be so provided in a year, and though in nature such a thing would rarely happen, the balance of retention and excretion over a series of years may tend either to increase the stores or to gradually diminish them.

When the fluctuation balances tend in the direction of increasing the stores, and the relation in excretion for a long period like fifteen years averages about 1—35 or 1—38, quite as much urate as I have ever seen in the human body may easily be accumulated.

As a matter of fact, in the colder months of the year acidity on any given diet tends to be high (I believe because there is but little loss of acids in perspiration from the skin—see Sir A. Garrod, previous reference, p. 258), and the balance of uric acid excretion tends to the side of retention or accumulation in the body; conversely, on the same diet acidity rules low in the warmer months (owing to loss of acids in perspiration), and the excretion of uric acid exceeds its formation, that is, more or less of the accumulations of the winter are washed out. Thus in 202 days of winter I got a relation of uric acid to urea 1--33, in 40 days of spring 1—30, and in 150 days of summer 1—29. This fact, that the excretion of uric acid is greater in the spring and summer months, has an important bearing on the seasonal variations of certain troubles that are due to uric acid (see "Mental Depression," &c.).

As already narrated (chapter i.), I very soon found that I was able to control the excretion of uric acid and increase or diminish it at pleasure.

That just as in nature the excretion of uric acid is small during the period of high urinary acidity at night, and large during the period of low acidity in the day, especially in the "alkaline tide" of the morning (fig. 1.), and, as we have also seen, small in winter and large in summer, so by giving acids I could diminish its excretion at any time, or by giving alkali could produce an artificial "alkaline tide" and a plus excretion.

I found, however, that my powers in either direction had limits, that, though I could produce a large excretion of uric acid at pleasure I could not keep up the large excretion very long, and could produce nothing that at all resembled an extra formation of uric acid.

If I produced retention for several days and then gave an alkali I could produce a much greater excretion than if there had been no retention beforehand.

On the other hand, if I gave salicylate of soda, and swept out a large amount of uric acid, an alkali given on the following days would produce no plus excretion whatever.

Again, if salicylate of soda was given in the same dose every day for a week there would be a large excretion on the first and second day, but after that the uric-acid curve would approach the urea and, with a few slight fluctuations, remain about the level of 1—33 or 1—35, which I have suggested is the level of formation.

It seems to me impossible to explain these facts on the supposition that there is in any of these cases an excessive formation of uric acid; if alkalies or salicylates cause an excessive formation this should continue from day to day, but it does not.

Hence I have concluded that all the fluctuations which occur in nature or can be produced by drugs, are fluctuations of excretion merely; I do not assert that excessive formation does not occur, it is proverbially difficult to prove a negative, but I have shown that it is probably unnecessary to assume its occurrence, and, even if it does occasionally occur, that does not alter the fact that all the diseases of which I shall presently speak may originate in retention or deficient excretion, without any excessive formation whatever.

Thus uric acid tends to accumulate in the body, as we have seen, in the cold months of the year, and to be excreted in excess in the warm months of the year, and these fluctuations may balance each other, there being no more urate in the body at the end of the year than there was at the beginning.

It is probable, however, as I have said, that during the vigorous nutrition of adult life up to and even past middle age, the acidity rules high, and year after year more uric acid is retained in the winter than is excreted in the summer, and the stores of urate in the body tend to increase; on the other hand, when from disease or in the natural course of events from old age, nutrition begins to fail, acidity falls and remains low, excretion of urate remains more or less permanently above formation as the urate accumulations of previous years are got again into solution in the blood, and passed through the kidney into the urine.

Since I first observed that I was able to alter the excretion of

uric acid from hour to hour or day to day at pleasure, I have investigated the effects of a very large number of drugs upon it, and I have summarised my results in the general statement that all substances which increase the solubility of uric acid increase its excretion, and clear it out of the body, while conversely, all substances which diminish its solubility diminish its excretion, and tend to produce its retention in the body and accumulation in various organs and tissues.

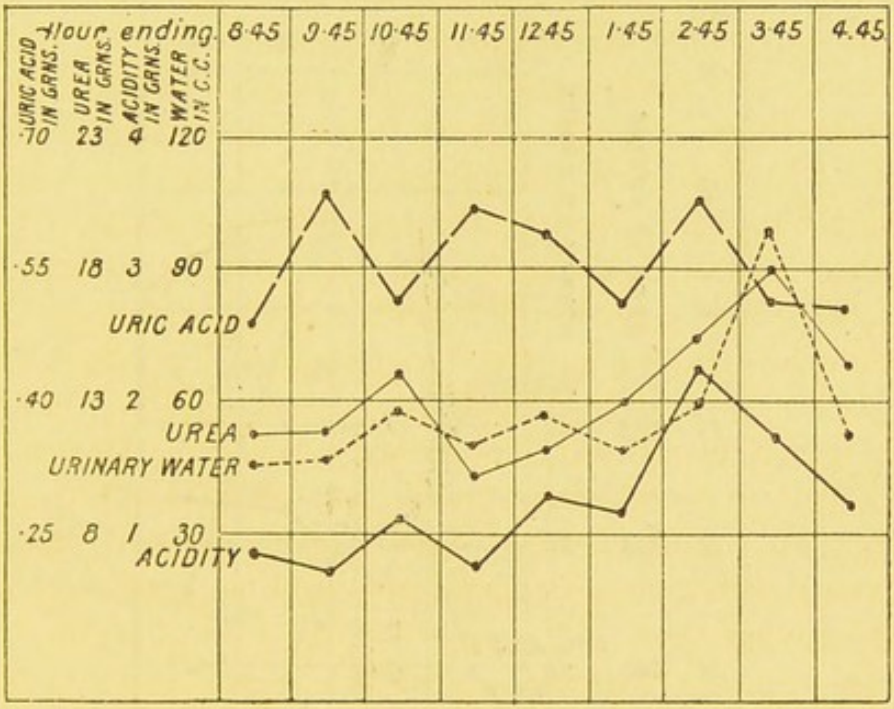

FIG. 1.—NATURAL PLUS EXCRETION OF URIC ACID IN THE ALKALINE TIDE.

Breakfast ended 9.50 A.M. Lunch ended 2.10 P.M. Two and a-half miles sharp walking 3.0 to 3.45 P.M.; perspiration, and low tension pulse after walk. Total urinary water 527 cubic centimètres. Total urea 118 grains. Total uric acid 5.0 grains. Relation of uric acid to urea 1 to 23.6.

And now in speaking of the action of drugs I shall divide them into (1) those that increase, and (2) those that decrease excretion, and having first enumerated those in each class shall say a few words as to the action of the individual drugs in turn.

The chief substances which increase the excretion of uric acid are alkalies, salicylic acid and its compounds, salicin salol, &c., phosphate of soda, piperazidin, and quinine.

I place alkalies first because they are found in action every day in nature, and hence have far greater importance than any

substances which are not in every-day action. The curves in figs. 1 and 2 show their effects.

Speaking generally, and apart from the action of other solvents, it may be said that the excretion of uric acid from day to day and hour to hour is inversely as the acidity of the urine.

And I think there is evidence to show that, speaking generally, the fluctuations in the acidity of the urine correspond both in

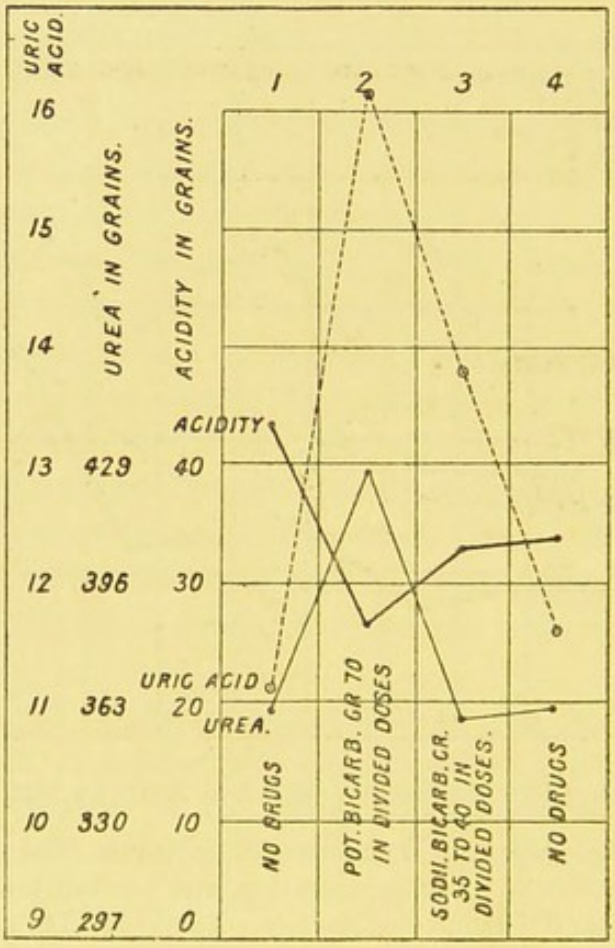

FIG. 2.—PLUS EXCRETION OF URIC ACID PRODUCED BY ALKALIES.

direction and extent with fluctuations in the alkalinity of the blood; thus it has been shown by Peiper (Virchow's "Archives," June, 1889, p. 337) and others, that the alkalinity of the blood is diminished in all fevers except such as are complicated by dyspnœa and cyanosis, and the acidity of the urine is increased in all fevers; a good instance of this fact being recorded in Sir W. Roberts' work "On Urinary and Renal Diseases," fourth edition (p. 59), where a patient with alkaline urine got erysipelas, and the

urine became acid and remained so during the fever, becoming alkaline again at the end of it.

Conversely a vegetarian diet is known to diminish the acidity of the urine, and I believe that it also increases the alkalinity of the blood.

Sir A. Garrod has shown that the alkalies, soda, and potash form extremely soluble compounds with uric acid, and phosphate of soda is also well known as a solvent of uric acid. (See fig. 3.)

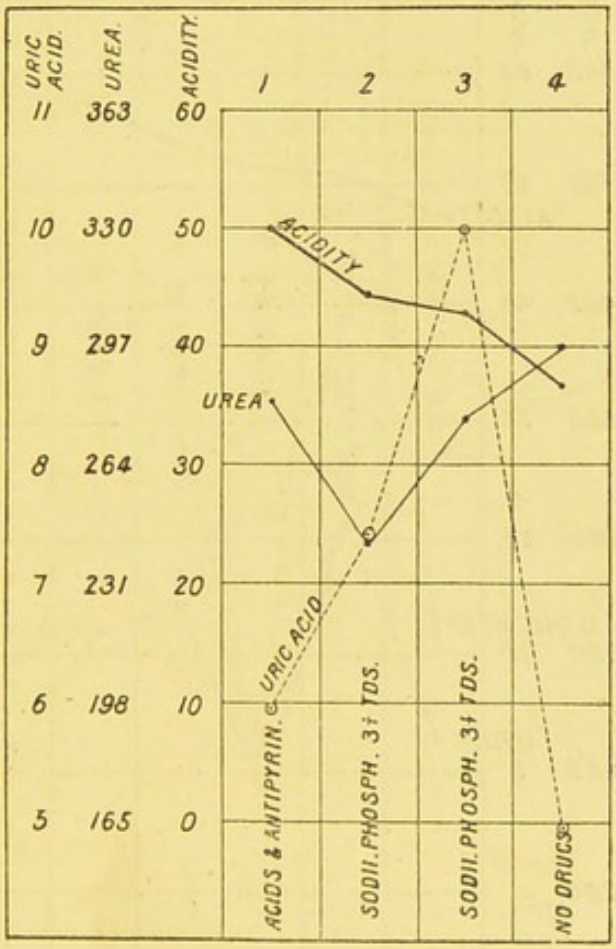

FIG. 3.—PLUS EXCRETION OF URIC ACID PRODUCED BY PHOSPHATE OF SODIUM.

As to salicylic acid and its compounds, I have shown that they increase the excretion of uric acid, and I have pointed out that what is known about the compound (salicyluric acid) which they form with it, points to its being not only more soluble in water than other salts of uric acid, but also much more soluble in slightly acid fluids—a very important point to which I shall often

have to refer again. Fig. 4 shows its action on excretion. This figure, and all the curves of excretion under salicylates show, I think, that we have to do with excretion and not with formation of uric acid; if salicylates cause new formation of uric acid, why does the curve never again reach the height attained on the first or second day though the drug is continued as before?

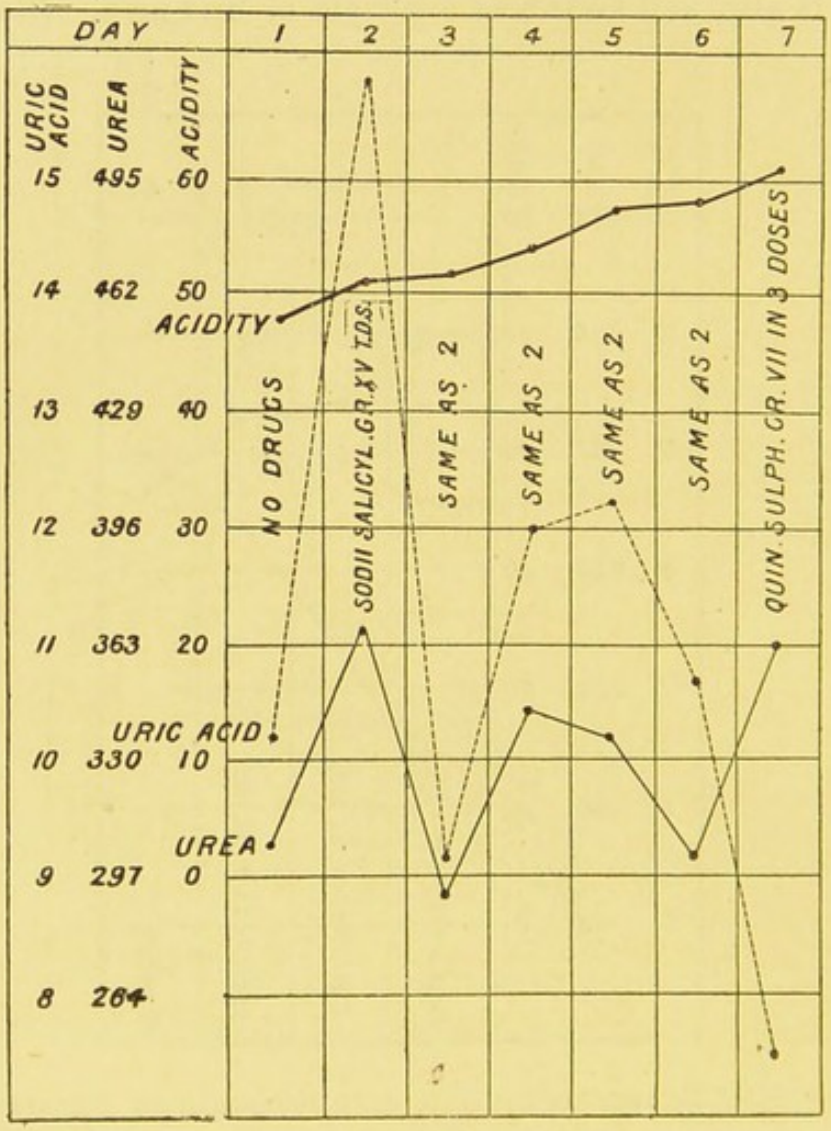

FIG. 4.—PLUS EXCRETION OF URIC ACID PRODUCED BY SALICYLATE OF SODIUM.

I have further shown that as regards acute rheumatism the salicyl compounds are powerful in curing the disease exactly in proportion to their power of eliminating uric acid; that, dose for dose, salicylates are most powerful in both respects, and are followed by salol, and at some distance by salicin.

Phosphate of soda, the ordinary Na_2HPO_4 is a good solvent of uric acid, and causes a plus excretion, but unlike the salicylates, it can only act in an alkaline medium, or while the supply of alkalies is abundant; the presence of any acid, or even of a salt of a mineral acid as a sulphate, appears to convert it into the acid phosphate NaH_2PO_4, and then there is no longer a plus excretion of uric acid.

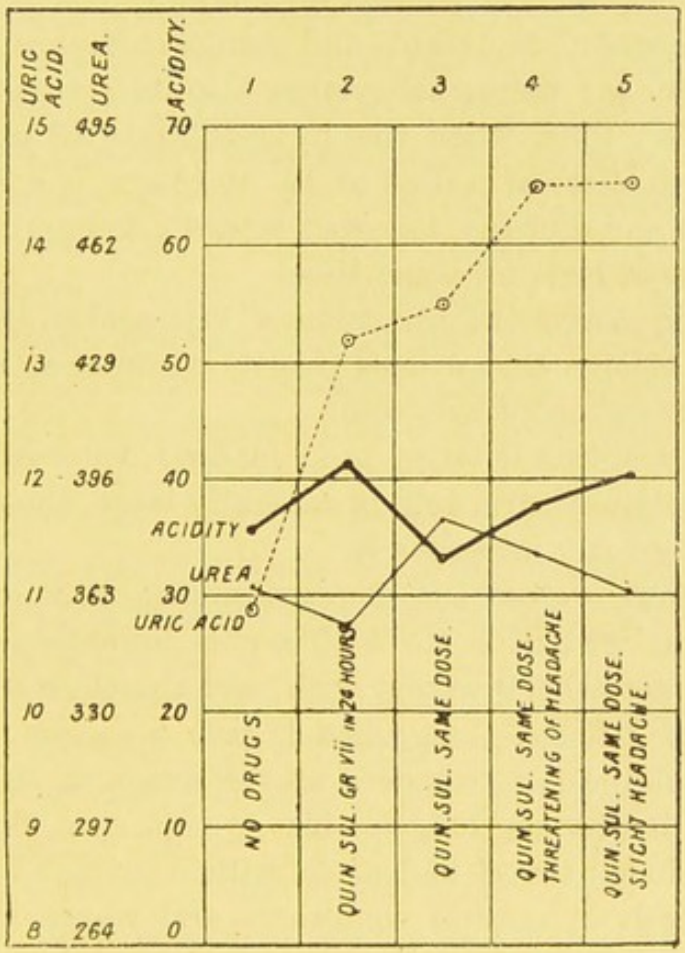

FIG. 5.—PLUS EXCRETION OF URIC ACID PRODUCED BY QUININE.

The practical point to remember, then, is that phosphate of soda should be given with alkalies, or in conditions when the supply of alkalies in the blood and tissue fluids is good, and it will then cause a satisfactory plus excretion of uric acid, as in headache, high tension pulse, and mental depression, when the alkalinity is high. Salicylates, on the other hand, act best; when the alkalinity is low, and their action as regards the excretion of uric acid appears to be absolutely hindered by the

presence of alkali, so that they do best in conditions of fever when the alkalinity is generally low, and in conditions where there is little or no fever, it may be necessary to give them with opium or ammonia which raise the acidity, or in alternate doses with acids to obtain their full effect on the excretion of uric acid, and not a few failures in the practical treatment of disease with salicylates are, I believe, due to ignorance of these facts.

I have made a few experiments with piperazidin and it appears to increase the excretion of urates, but it is certainly not a very powerful excretant, and cannot compare with salicylates for instance; unlike salicylates also its action is interfered with by acids; thus, when the hydrochlorate of piperazadin is taken the first effect of a dose of 12 to 15 grs. is a minus excretion of urate and diuresis, followed later by some plus excretion, which, however, lasts for some time.

Quinine increases the excretion of uric acid in the urine (see fig. 5) and I believe that it does this by contracting the spleen, a well-known reservoir of uric acid.

Where the spleen is large, as in malaria, leucocythæmia, &c., and the excretion of uric acid is generally large, the exhibition of quinine very greatly increases it.

When I first noticed the increase of uric acid under quinine I thought that we had to do with a plus formation of uric acid which I had not otherwise met with, and therefore regarded with interest; but I found that when I gave a course of salicylate before the quinine (*i.e.*, removed all the available uric acid from the spleen) it was no longer able to cause a plus excretion, hence I concluded that I had to do with excretion and not with formation, both in normal conditions and where the spleen is enlarged.

When quinine squeezes the uric acid, as we are supposing, out of the spleen, it produces more or less uricacidæmia, and the signs of this blood condition are among the prominent symptoms of quinism. Thus, the headache which quinine produces in many people is well known. I have pointed out that quinine is said to do harm in epilepsy, or may even produce epilepsy; it is also recorded that quinine given in large doses for malaria may produce hæmoglobinuria (*Progrès Medicale*, July, 1888, p. 4), and for my arguments about this latter trouble see chapter xii.

I have several times met with patients with large spleens who

objected strongly to taking quinine, as they said it always gave them a bad headache, and this is just what I should expect (see also *Brain*, Spring number, 1891, p. 73). And Dr. Lauder Brunton, in a most favourable mention of my work ("Cavendish Lecture," 1891, *Lancet*, vol. i., 1891, p. 1361), says that it enabled him to understand how a patient under his care with a very large spleen was able to keep on passing uratic gravel. Dr. Brunton had almost concluded that he must have a stone in his bladder, of which portions were being excreted, but after death no stone was found. No doubt this patient was passing a great excess of urate, having a relation to urea of 1—10 or 1—12, and some of this would, from time to time, from absence of pigment or salts or excess of acids, &c. (see Sir W. Roberts, *Medico-Chirurgical Transactions*, vol. lxxiii., p. 266), be deposited in the urinary passages, so that our knowledge of the formation and excretion of urates is likely to throw some light on the formation of calculi (see also *Lancet*, February, 1888, p. 1010, for a case in which there was a large spleen and a urate calculus was quickly formed).

Ranke and others state that quinine diminishes the uric acid in the urine, and this statement being diametrically opposed to my own results puzzled me for some time, but I now believe that it can be easily explained.

Sulphate of quinine has a double action on uric acid, that is to say, it has the action of a sulphate, which, as I shall show presently, causes retention of uric acid and clears it out of the blood, and then it has the action on the spleen, causing uric-acidæmia and a plus excretion of uric acid.

If a small dose (6 grs. in twenty-four hours) of sulphate of quinine is taken and its effects are watched from hour to hour, what is seen is this: there is first of all a rise of acidity of urine, a minus excretion of uric acid, a relaxation of arterioles and a plus excretion of water (diuresis); later on acidity falls and uricacidæmia sets in; with this there is slower pulse, diminishing urinary water and a tendency to headache, and generally with small doses the second stage of uricacidæmia and plus excretion outweighs the minus excretion of the first stage; but with large doses of sulphate—6 to 15 grs.—(and Ranke and others specially mention large doses), the effect of the sulphate would be more powerful and lasting, and the minus excretion of

uric acid, with reduced arterial tension and diuresis, might continue a whole twenty-four hours or more, hence the difference between my results and those of others is due to difference of dose, and is apparent rather than real.

The chief substances which diminish the excretion of uric acid are acids, iron, lead, lithia, manganese, calcium chloride, acid phosphate of soda, some sulphates, chlorides, &c., and many substances which directly or indirectly raise the acidity, or other-

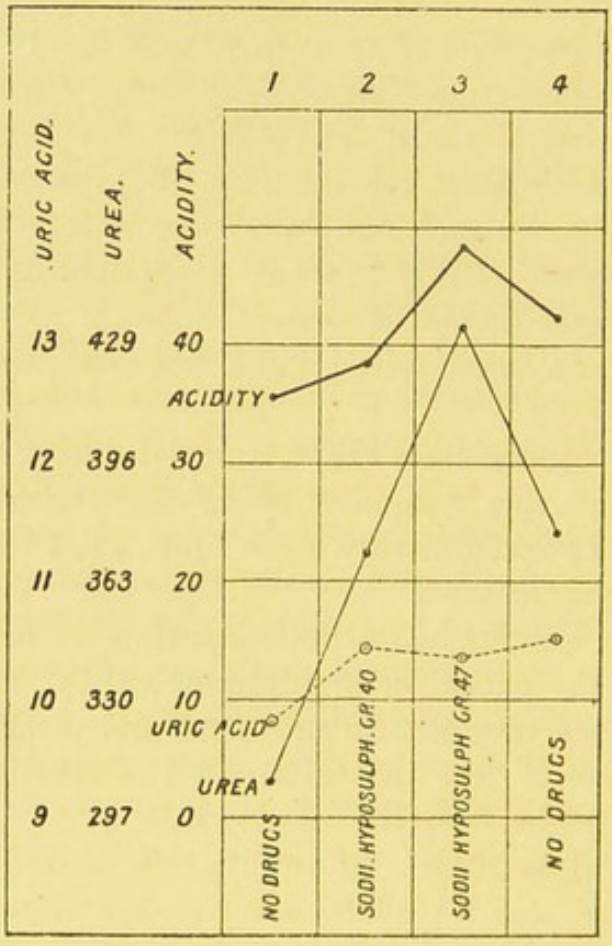

FIG. 6.—RETENTION OF URIC ACID PRODUCED BY ACIDS.

wise form insoluble compounds with uric acid, as opium, cocaine, mercury, the iodides, antipyrin, ammonium, the nitrites, some hyposulphites, strychnine, and many other less well-known substances.

All these substances diminish the excretion of uric acid, and bring about its retention and accumulation in the body. They clear it out of the blood and produce the symptoms of its absence

from the circulation, which are for the most part the reverse of those produced by its presence. They drive the urates out of the circulation into the joints and fibrous tissues, where its arrival may be evidenced by pricking and shooting pains (see gout), also into the liver, spleen, and other organs.

I place acids at the head of the list because their action dominates the physiology of every-day life, and their range of action is therefore infinitely more extensive than that of the other members of the list whose presence is more or less accidental and temporary (see fig. 6).

Acidity of urine bears, as I have shown, a fairly constant relation to urea, both tending to rise and fall together, and the relation I have given, 1 of acidity (reckoned as oxalic acid) to 6.1 of urea, is very constant. Whatever (food, exercise, &c.) raises urea raises acidity, and *vice versâ ;* thus a meal of mutton or beef will increase urea, and it has been suggested by some authors that the concomitant rise in acidity is due to the salts contained in the meat (Senator, *Ziemssen*, vol. xvi., pp. 126-7). Thus meat not only increases the formation of urate but interferes with its excretion and promotes retention, and we shall see presently, that it also introduces urate ready formed into the body. Then acids are contained in many articles of diet, and especially in wines, beers, and other drinks, cider, lemonade, &c. Sir A. Garrod, it may be remembered, attributed the gout-producing powers of beers and certain wines to some unfermented matters they contained, but I have shown (*British Medical Journal*, vol. ii., 1888, pp. 10-11), that the acids they all contain in very large quantity, and without which beers, for instance, would neither keep good nor be palatable, quite sufficiently account for their gout-producing powers. Acids, again, may be formed by certain fermentation processes in digestion, a question which M. Bouchard has very ably worked out (*Leçons sur les Auto-Intoxications*, p. 172).

Sir A. Garrod has shown (prev. ref., p. 258) that suppression of perspiration is immediately followed by a rise in the acidity of the urine, and I can prove that increase of perspiration diminishes the acidity of the urine. Hence we can explain how hot rooms or warm south-west winds diminish the acidity of the urine, increase the excretion of uric acid, and produce the feelings of languor and depression which are due to its presence in the

circulation; also how a cold north-east wind raises the acidity and produces the reverse effect, making us cheerful and brisk.[1]

Last, but not least, deficient oxidation lowers acidity. I have previously mentioned that according to Peiper fevers accompanied by dyspnœa and cyanosis form exceptions to the rule that fever raises the acidity of the urine and diminishes the

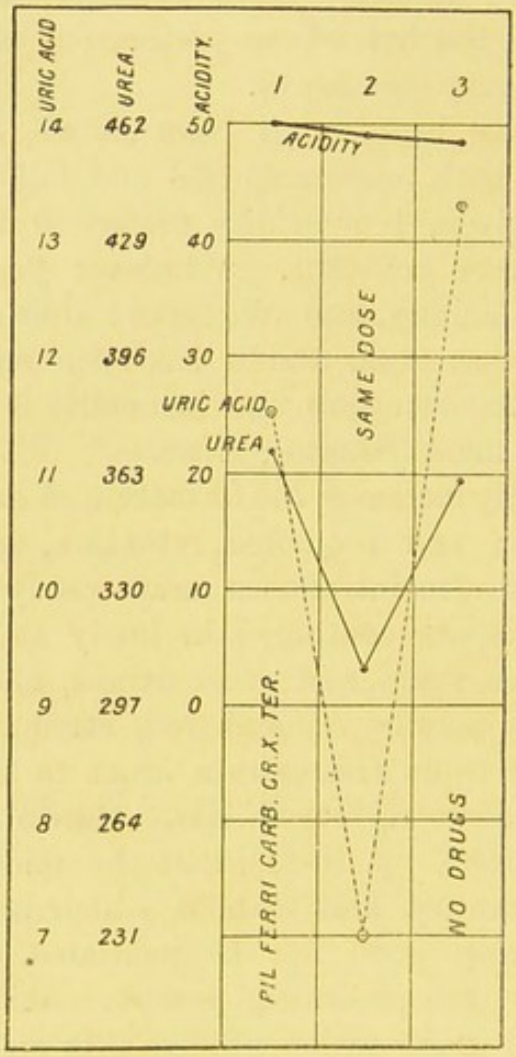

FIG. 7.—RETENTION OF URIC ACID PRODUCED BY IRON.
From *Med. Chi. Trans.*

alkalinity of the blood, and it seems to me that deficient oxidation must mean deficient formation of acids (see *St. Bartholomew's Hospital Reports*, vol. xxvi., p. 19 of my paper), hence the cause of the above exception to the rule.

[1] As to the fact that sweat at the time of its discharge from the ducts is normally acid, see *Heuss Monatschr. fur prakt Derm.*, No. 9, 1892.

I have very little doubt, therefore, that many of the headaches which people suffer from after theatres, church, and other meetings are due to the heat and deficiency of oxygen, both of which lower the acidity of the urine, increase the alkalinity of the blood, and flood it with any uric acid that may be at hand ready to be got into solution; but as I have said before, if all the available uric acid has been previously removed, none of these conditions will

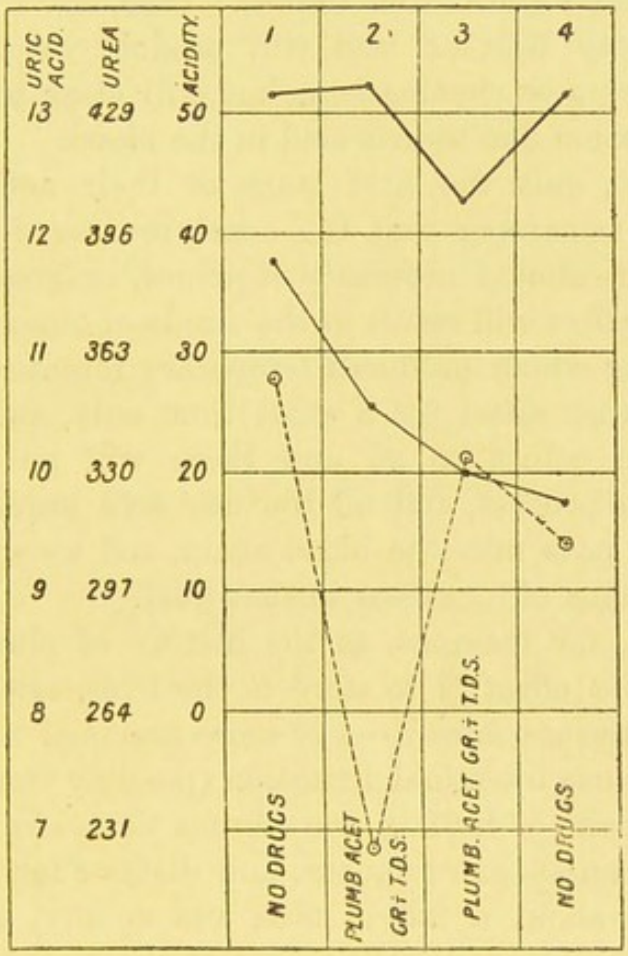

FIG. 8.—RETENTION OF URIC ACID PRODUCED BY LEAD.
From *Med. Chi. Trans.*

have any effect, and a knowledge of these simple facts about uric acid enables me to explain hundreds of sequences in the physiology and pathology of everyday life, of which I can only mention a very few here.

With regard to *iron and lead*, Sir A. Garrod has shown that these substances form insoluble urates, and they therefore fall at once within my rule, and diminish the excretion of uric acid

because the compounds they form with it are insoluble, just as salicylates increase its excretion because they form soluble compounds with it.

The first effects, then, of iron and lead are to diminish the excretion of uric acid and clear it out of the blood, and at this stage they produce on the one hand the symptoms which we shall presently see are due to its absence from the blood, and on the other the pricking and shooting pains which indicate its presence in joints and fibrous tissues. (See figs. 7 and 8.)

In this way iron or lead will produce or precipitate the arthritis of gout or rheumatism, but will clear up headache or mental depression due to uric acid in the blood.

But this is only the first stage of their action, and it is necessary to remember that the exact reverse of this condition of things is an almost necessary sequence, or great confusion as to cause and effect will result in the minds of observers.

Every drug which produces temporary retention of uric acid can produce that effect for a short time only, and when its retentive action comes to an end there will be a rebound or reversal of the process, and all the uric acid previously retained will begin to pass into the blood again, and we shall once more have all the signs of its excess in that fluid.

Take lead, for instance, as the history of plumbism is well known; its first effect is to store in the liver, spleen,[1] joints and other fibrous tissues some 3—4 or more grains of uric acid; then it begins to cause intestinal irritation (possibly from a deposition of insoluble urate of lead in the fibrous tissues of the intestinal walls); this causes pain, nausea, and distaste for food, and this quickly brings about a fall in urea and acidity, and the rising alkalinity of the blood dissolves part of the 3 or 4 grs. on store, and floods the blood with uric acid; hence along with lead colic we have headache, depression, slow high tension pulse, and perhaps even epilepsy—all due as I shall show, to the excess of uric acid in circulation; and anyone who will take the trouble to experiment with lead as I have done, can produce not only the fluctuations in uric acid (first, a retention, and then a plus excretion), but also all the signs and symptoms of its presence or absence from the blood just in the sequence I have mentioned

[1] See "Lead Poisoning," by Professor T. Oliver, p. 102, *et seq.*; Young J. Pentland, 1891.

them, and I have no doubt that any clinical observer will bear me out if I say that these are the main symptoms of acute and chronic plumbism which can thus not only be explained but can be imitated at pleasure, either with lead itself or other members of the group, such as opium, cocaine, mercury, or acids.

Indeed, to such an extent is this the case, that I have come to believe that many cases of intestinal colic are due to urate

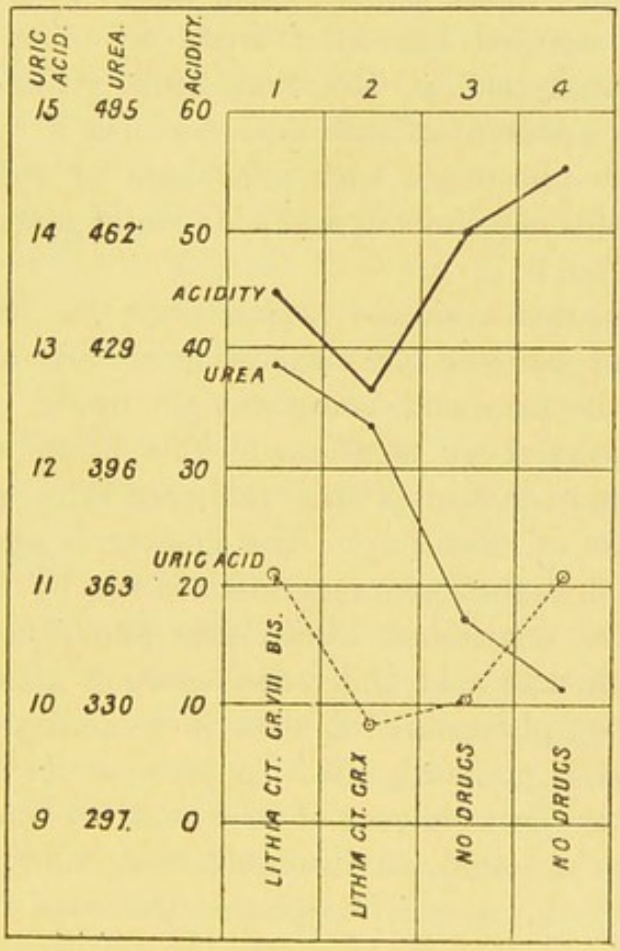

FIG. 9.—RETENTION OF URIC ACID PRODUCED BY LITHIA.
From *Med. Chi. Trans.*

irritation, of which urate of lead affords but a single instance, and in corroboration of this I may mention that salicylate of soda is a valuable remedy in all these forms of colic—a discovery which I made quite accidentally in my own case. (See chap. x.).

About lithia also I must say a few words, because it is an apparent exception—an exception, however, which beautifully proves the rule I have stated.

Sir A. Garrod has shown that urate of lithia is one of the most soluble of all urates, and yet I found that lithia diminished the excretion of uric acid. (See fig. 9.[1])

I may frankly confess that if I had been unable to find an explanation of this fact, I should long ago have given up my quest, and regarded uric acid as an insoluble enigma or will-o'-the-wisp, but fortunately the difficulty had already been solved for me by others, for in a reference which I owe to Dr. Neale's "Digest" to the *Lancet*, 1860, vol. ii., p. 185, I found that it had been pointed out in a work on chemistry by Rose ("Chemical Analysis," p. 15), that lithia given by the mouth was no use as a solvent of uric acid, because it "forms a nearly insoluble triple phosphate with phosphate of soda, or with the triple phosphates of ammonia and soda, salts generally present in animal fluids."

Here, then, was a simple explanation; the lithia I took by mouth did not cause a plus excretion of uric acid because it never got to the uric acid, being waylaid by the phosphates and triple phosphates above mentioned; this would explain its not causing a plus excretion of uric acid, but why does it cause a minus excretion or retention? The answer is again simple, and it was in the first instance suggested to me by Mr. J. E. Saul, F.I.C. I have mentioned before that phosphate of soda is a good solvent of uric acid and in presence of alkali increases its excretion; now phosphate of soda is a normal constituent of the blood, and is generally there in presence of alkali, *i.e.*, in a condition to act as a solvent of uric acid, so that the lithia in forming, as we are told, an insoluble compound (well known to chemists) with the above phosphates, removes from the blood one of the natural solvents of uric acid, and we now see not only why lithia causes no plus excretion of uric acid, but why it causes retention, and there is here no exception whatever to my law of solubilities.

In the test tube lithia is said to be a beautiful solvent of uric acid, but in the body its chemical combinations with phosphates not only prevent its action on uric acid, but put out of use a certain amount of phosphate also.

A year or two ago, at the suggestion of Sir Dyce Duckworth

[1] This fact is corroborated by the observations of Professor Oliver, "Lead Poisoning," p. 107.

(see "A Treatise on Gout," p. 373), I investigated the action of manganese on the excretion of urates, and I found that it produced retention and some pains in the joints; so that it acts like calcium, iron, lead, mercury, and other metals, which form insoluble compounds with uric acid and probably for the same reason.

Urate of calcium is very insoluble,[1] and chloride of calcium has an acid reaction, hence it probably diminishes the excretion of uric acid in two ways. I was led to observe that it did this by noticing that when administered internally it generally produced, to a very marked extent, a condition of happiness, well being, and good temper, which, as we shall see presently, is a sign of absence of uric acid from the blood.

I note also that Dr. G. Thin (*British Medical Journal*, vol. ii., 1891, p. 91) holds the opinion that the consumption of water containing lime brings about the development of gouty conditions; no doubt it acts in the same way as the contamination of water by lead; but if people would be at the trouble to reduce their nitrogenous metabolism, and so their formation of uric acid, neither lime, lead, acids, or anything else would be able to injure them.

Acid phosphate of soda, or ordinary phosphate of soda given with a little phosphoric acid or in conditions of high acidity, brings about retention rather than plus excretion of uric acid.

In a similar way the salts of the mineral acids, sulphates, chlorides, &c., raise the acidity of the urine and produce a minus excretion or retention of uric acid; possibly they, to some extent, produce this result by changing the phosphates of the blood into acid phosphates, in which condition they are no longer able to act as solvents of uric acid, and I was able to show that while neutral phosphate of soda is a good solvent and produces a plus excretion of uric acid, it is unable to do this if a small quantity of sulphate of soda is given along with it (*Medico-Chirurgical Transactions*, vol. lxxii., p. 402).

Of opium (see fig. 10) I have elsewhere (*British Medical Journal*, November, 1889) written at considerable length, showing that it raises the acidity of the urine, probably by increasing the absorption of acids from the intestines, and when it does this

[1] One in 2,800 parts of water; Sir A. Garrod's Lectures, *British Medical Journal*, January, 1883, p. 495.

it diminishes the excretion of uric acid and stores it in the liver, spleen, and joints, in the latter of which it may cause pricking and shooting pains; it also produces the symptoms of absence of uric acid from the blood, namely, mental brilliancy, happiness, well-being, and good temper, for which it is so often resorted to. As with other members of this group (see previous remarks on

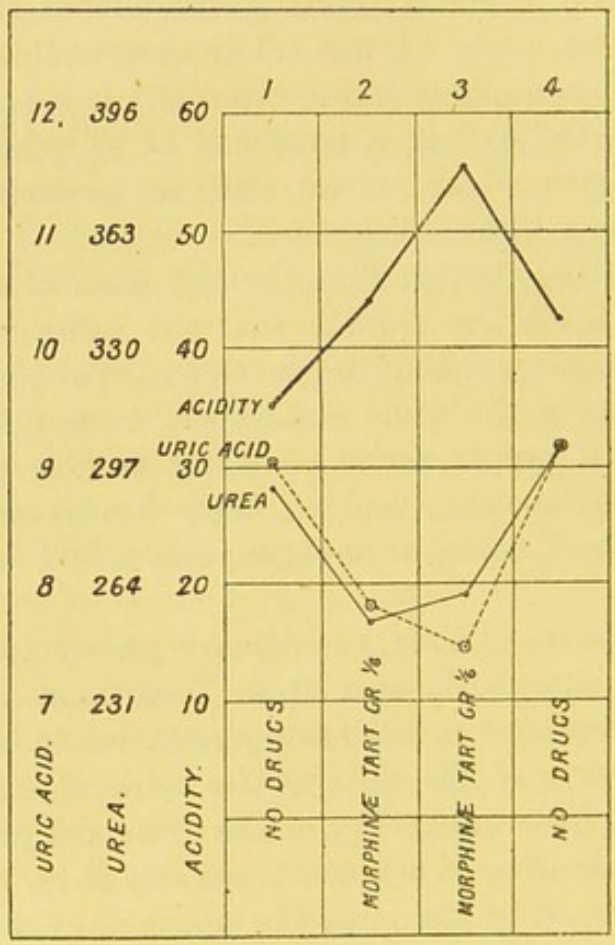

FIG. 10.—RETENTION OF URIC ACID PRODUCED BY MORPHINE.

The dose of morphine was taken at 11 P.M. on Day 2, and at 8 A.M. on Day 3. It raised the acidity of both days, but affected the alkaline tide only on Day 3.

lead), its first action is followed by a rebound, in which the blood is flooded with uric acid, and the signs of its excess are seen in the headache, depression, and general misery, with slow high tension pulse which accompany this second stage of opium action (see fig. 23). These symptoms of mental misery and depression are those which drive the victim of the morphine habit to repeat his dose, to obtain once more the first-stage action of

opium and temporary relief from his mental misery. I have pointed out that, in accordance with this reasoning, if salicylate of soda is given along with or in sequence to the first dose of opium, it prevents the opium causing any retention of uric acid, and then the opium rebound on the following day fails to appear or is very greatly modified.

This has led me to suggest (*British Medical Journal*, November, 1889) the use of salicylates to aid the throwing off of the morphine habit, and I know of at least one case where my suggestion has been followed with advantage.

A medical man, who had been in the habit of taking morphine for some time since a severe and dangerous illness in which it was used, wrote to me after the appearance of my article in the journal as to the best way of leaving it off, and I suggested, among other things, a plan of using the salicylates.

I have since heard from him that the plan was quite successful, that he was surprised how easily he was able to leave it off, and that he had no insomnia, and he ends by saying, "I shall always remember you with gratitude as having shown me the way to give up the habit, and I am sure that without the salicylates I should only have been able to do so with the greatest difficulty." How far other cases will bear this out remains to be seen.

In my own person a dose or two of salicylates after a dose of opium completely prevents what I call the opium rebound, and there is no headache, depression, or other ill-effect from the drug next day, but I have not myself tried it except after small doses of opium and morphine, not continued for more than a day or two.

The action of cocaine, so far as uric acid is concerned, exactly resembles that of morphine, and like morphine it produces a first stage of happiness and well-being, followed later by a second stage of misery and depression, and cocaine has been indulged in to excess in the same way and for the same reasons that morphine has.

In my own case cocaine soon produces severe intestinal colic, so much so that I have been unable to continue or repeat my experiments with it as often as I should otherwise have done, but there is no doubt that it affects uric acid in the same way that morphine does, and produces identical feelings of happiness and well-being—indeed, each member of the group of drugs which

diminishes the excretion of uric acid produces these feelings to a more or less marked extent.

The first action of cocaine, like that of morphine, is to produce a low tension and quick pulse, due to relaxed arterioles, and the result of this is, on the one hand, improved and quickened circulation in the brain, with mental brilliancy and well-being, and on the other relaxation of the vessels in the kidney causing a marked diuresis of a pale and watery urine.

Later on, just as with opium and other drugs I have spoken of, there comes a rebound. The uric acid held back and cleared out of the blood by the first action of the drug is again got into solution, the arterioles are strongly contracted and the tension high, hence the urine is scanty and of high specific gravity, and the mental condition one of lethargy and depression, with sleepiness (as in all high tension), and these miseries drive the sufferer to repeat the dose to get its first-stage action once more, and so lead the way to chronic cocainism.

I have very little doubt that cocaine, like morphine, owes a large part of its effects to its action on uric acid, and that salicylate of soda may be useful in cocainism just as in morphinism. For some interesting facts about the action of cocaine see Dr. A. Fullerton, *Lancet*, February, 1891, p. 663.

CHAPTER III.

Formation and Excretion of Uric Acid (*continued*).

Mercury is another very interesting member of the group of drugs which cause retention of urates. I have already written about it elsewhere (see *British Medical Journal*, vol. i, 1890, p. 1241).

Fig. 11 shows very well its action on uric acid, which on Day 1 is a little below urea; on Day 2 as the effect of half a grain of calomel it is far below urea, and on Day 3, when no drugs are given, it bears about the same relation to urea as it did on Day 1. Note also the very marked diuresis on Day 2, corresponding with the greatest retention of urate, its clearance out of the blood, and consequent relaxation of arterioles (see chapter v.).

Mercury sometimes causes, in my own case, considerable intestinal pain and colic, like that produced by cocaine, lead, &c.

I have also suggested that the low arterial tension and the diuresis, which are well known to be brought about by the action of mercury, are due to its effects on uric acid, for other drugs having similar effects on uric acid produce similar symptoms as we shall see.

With regard to the action of mercury, Sir A. Garrod does not, so far as I know, say anything as to the solubility of urate of mercury, and it is not mentioned in his table of solubilities of urates (*British Medical Journal*, vol. i., 1883, p. 495).

It seems to me, however, that it is very probable that mercury causes retention of uric acid, and clears it out of the blood for the same reason that iron and lead do so, namely, that their urates are insoluble, and Mr. J. E. Saul, F.I.C., has kindly given me the following statement as to the solubility of the urates of mercury:—

"I find that a solution of neutral lithium urate, treated with solution of mercuric chloride, yields a curdy white precipitate practically insoluble in cold water. On boiling, slight decomposition occurs, the precipitate becoming yellowish—possibly owing to the formation of an oxysalt. On treating the first-mentioned precipitate with acetic acid, or a trace of hydrochloric acid, solution, slowly in the former case and immediately in the latter, takes place. Borax or alkalies exercise no solvent action. These

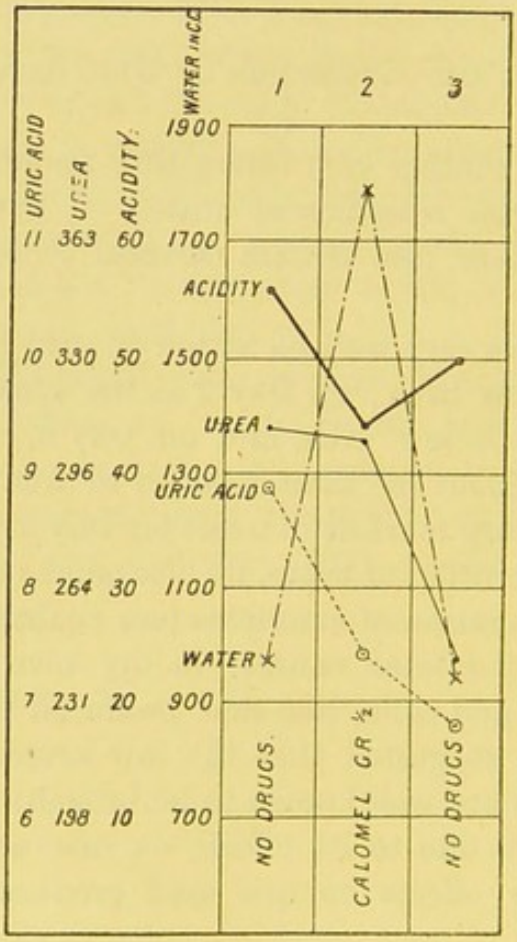

FIG. 11.—RETENTION OF URIC ACID PRODUCED BY MERCURY.

Note that on Day 2 uric acid falls in spite of a marked fall in acidity, which, apart from the action of mercury, would have made it rise.

experiments show that neutral mercuric urate is insoluble, but that the salt will dissolve in the presence of acid, though doubtless with decomposition.

"I have also examined the behaviour of a neutral alkali urate with solution of mercurous nitrate. I find that a yellowish precipitate, insoluble in water, is immediately produced; the pre-

cipitate rapidly darkening in colour, and ultimately becoming grey-black from reduction. In the presence of nitric acid no precipitate is obtained, but if acetic acid be substituted, a partial precipitation slowly takes place.

(*Signed*) "J. E. SAUL."

From this we see that there is good reason to believe that the urates of mercury are insoluble in water, in neutral solutions, in alkalies, or in solution of borax, and as the blood may be practically regarded as an alkaline solution, they are probably insoluble in the blood.

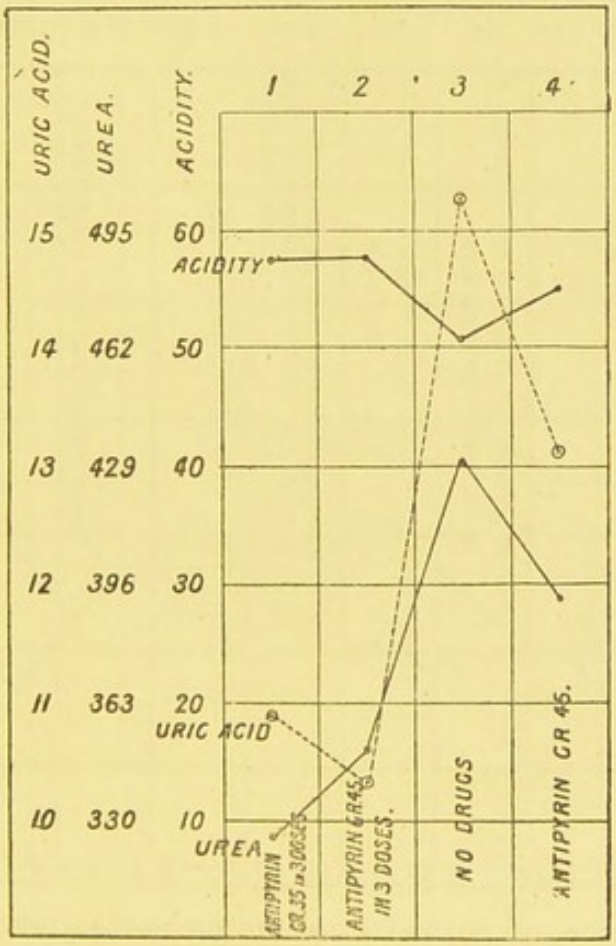

FIG. 12.—RETENTION OF URIC ACID PRODUCED BY ANTIPYRIN.

Therefore, mercury diminishes the excretion of uric acid in the urine, clears it out of the blood, and retains it in the body, because it forms with it an insoluble compound, and it is therefore a single instance of my law of solubilities. And the well-known action of mercury on the pulse-rate and tension, and the flow of urine, are also single instances of the laws I have formulated with regard to the relation of these to uric acid.

I think it is extremely probable that the urates of other metals, such as zinc and silver, are also insoluble, and indeed Haycraft's process for the estimation of uric acid depends upon the insolubility of the urate of silver, and that the so-called tonic action of these drugs, as of iron and manganese, and indeed of acids, is really due to their clearing the blood of uric acid, and so improving the circulation in the brain and other portions of the nervous system. It is interesting to remember that zinc, like

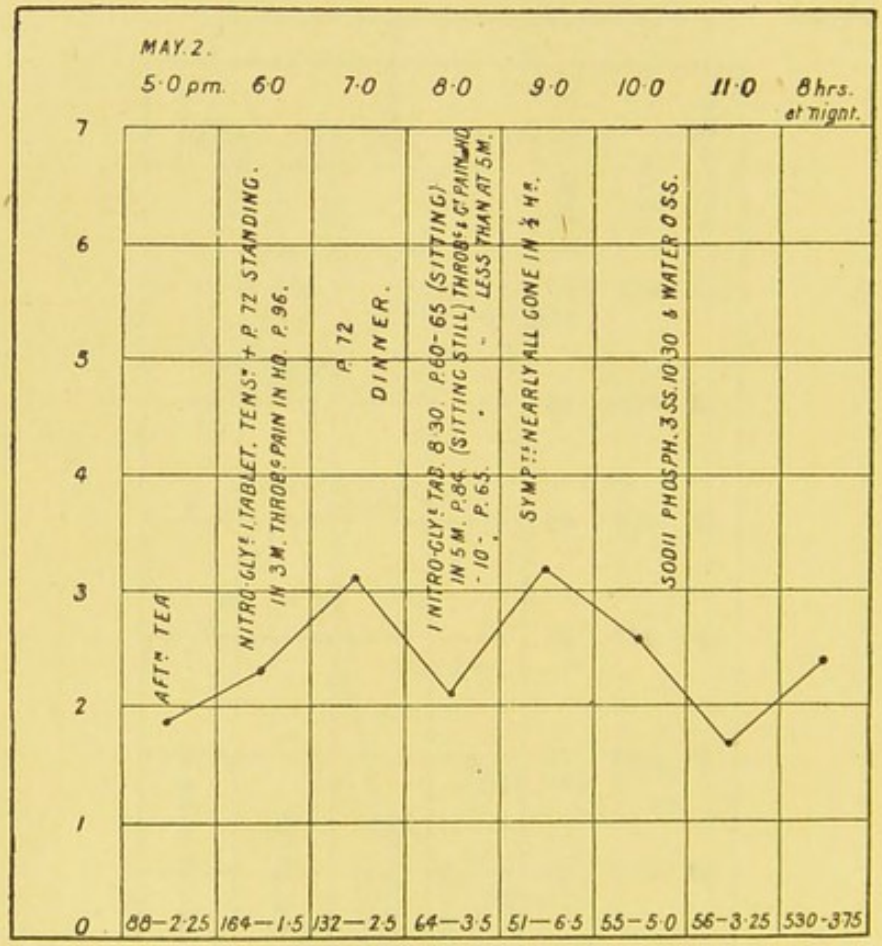

FIG. 13a.—EFFECTS OF NITRO-GLYCERINE ON THE ACIDITY OF THE URINE.

mercury and lead, may produce colic (Ringer, "Handbook of Therapeutics," ed. xii., p. 254).

I have suggested that antipyrin cures headache by acting as an acid, and its administration is always followed by a rise in the acidity of the urine.

Fig. 12 shows the effects of antipyrin on the acidity, which on Days 1 and 2 rises and remains high, and with this on Day 2 uric acid falls below urea (probably the antipyrin came too late to

affect the alkaline tide of Day 1, so that the greater part of the urate excretion had already taken place). On Day 3 no drug is taken, and acidity falls decidedly, in spite of the fact that urea has risen, and in normal conditions acidity would have risen also; but the antipyrin had raised it so much on the previous days that the moment it was withdrawn down it fell. On Day 4 antipyrin was again given, acidity rose in spite of falling urea, and uric acid was brought down much nearer urea.

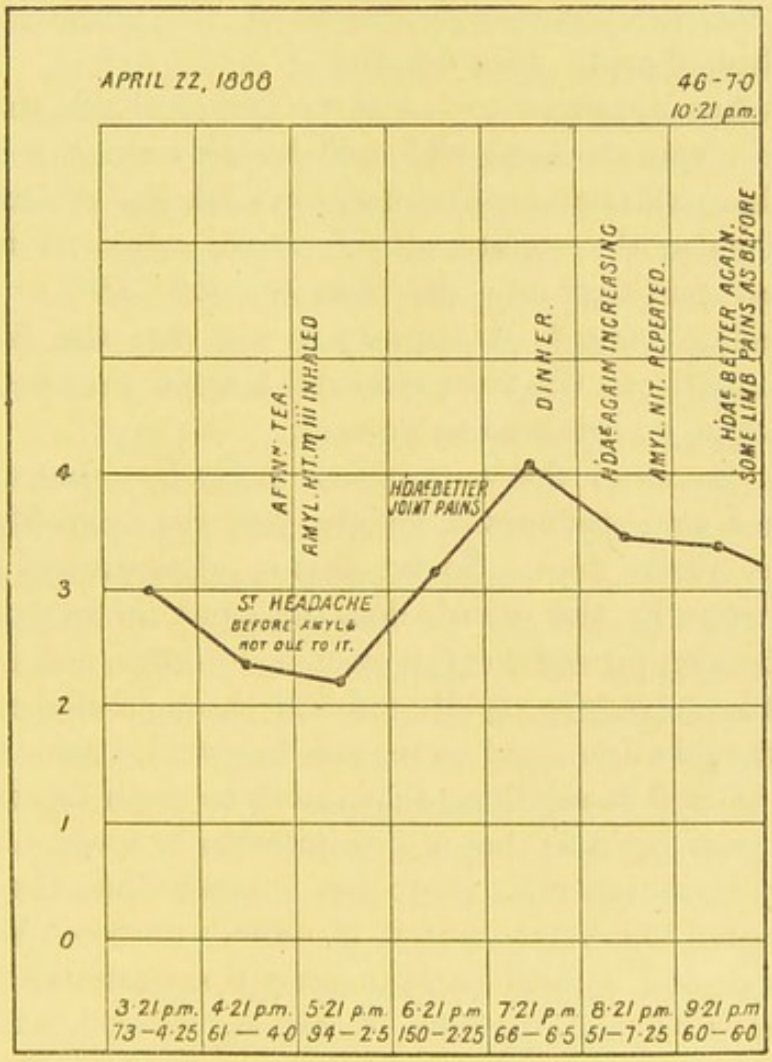

FIG. 13β.—EFFECTS OF NITRITE OF AMYL ON THE ACIDITY OF THE URINE.

We can now see how antipyrin cures a uric acid headache, by raising acidity and clearing the blood of uric acid, all the signs of which mental well-being, low tension, quick pulse, joint pains and diuresis it also produces; it therefore acts just as an acid, and I for one should prefer to give an acid in its place.

Strychnine causes a marked rise in urinary acidity and cures headache. I have suggested that the rise of acidity is due to its improving the condition of the stomach and promoting digestion and absorption of food, which in headache with nausea is often at a standstill; like other things that raise acidity, it often causes pricking and shooting pains in the joints.

The administration of hyposulphite of soda produces a very marked rise in acidity of the urine, possibly by the formation of sulphurous acid or the further oxidation of sulphur, and it produces all the symptoms and effects of the administration of a strong dose of acid. (See fig. 6.)

And it has appeared to me to be very probable that nitrites may act in much the same way, and by the formation of nitrous acid or other oxidation product may diminish the alkalinity of the blood and raise the acidity of the urine, which it is easy to demonstrate that they do. (See figs. 13*a* and 13*β*.)

This being granted, it appears to me that the well-known effects of nitrites on the pulse rate and tension may be explained by their action on uric acid as an acid.

And in favour of this supposition is the fact that an acid injected into a vein produces, I believe, just the same effect on the pulse as a nitrite does. So far as my observations go, nitroglycerine taken by the mouth does not exert its maximum effect on pulse tension for some seven or eight minutes, and in the case of a volatile substance rapidly diffused throughout the body this is a considerable time; and as regards uric acid, I take it that the action of an acid or anything that interferes with its solubility in the blood is as rapid as that of precipitation in a test-tube, and is practically instantaneous. I do not suppose that the uric acid is precipitated in crystals, but it is rapidly rendered less soluble in the fluids and is held back in certain organs and tissues in accordance with the theories of Sir A. Garrod, and I shall presently have to bring forward evidence that anything which clears the blood of uric acid allows the arterioles all over the body to relax, and rapidly reduces blood-pressure, the rapidity of the relaxation depending on the rapidity and completeness with which the uric acid is driven out.

In the *Lancet* (vol. i., 1891, p. 1323), it is pointed out that the administration of sulphurous acid, and even its inhalation, will reduce the alkalinity of the blood, which is greatly in favour of

my argument as to the action of nitrites, and my results as regards the acidity of the urine when hyposulphites or sulphur in other forms is taken. The same article shows that sulphurous acid is largely used in the preservation of wine and vegetables—a fact of considerable importance for gouty subjects.

It is certainly remarkable what very small quantities of these acids (nitrous, sulphurous, &c.) will produce marked effects on the excretion of uric acid, and in this they do not stand alone, for quite small quantities of salts of the mineral acids will produce similar effects, as I have had experience in very numerous instances. And thinking over this matter, it has occurred to me that the solvent power of phosphate of soda for uric acid and urates may help us to explain this apparent difficulty, just as they helped us to explain the difficulty in the case of lithia. If a little lithia produces marked retention of uric acid by throwing out of action a quantity of its natural solvent, phosphate of soda, a minute quantity of acid may possibly have the same effect on the phosphate, and may change a large quantity of it from $Na_2H.PO_4$ to NaH_2PO_4; then the effect on the solubility of the urate will be proportional to the amount of phosphate which is thus thrown out of action, and not to the relatively minute amount of acid which caused the change.

With regard to the action of the nitrites, the researches of Professor Leech (Croonian Lectures, 1893) seem to show that those substances undoubtedly exercise a direct depressant action on muscular tissue. They also show, however, that these compounds are decomposed in the stomach, giving off nitrous acid, which is absorbed into the blood and importantly affects its composition and reaction; thus Professor Leech says (*Lancet*, vol. i., 1893, p. 1502), "When absorbed it (nitrous acid) is no doubt at once converted into an alkaline nitrite, for it can replace carbonic acid in its sodium compounds and convert normal sodium phosphate into acid phosphate, sodium nitrite being at the same time formed."

Now, the result of this conversion of normal phosphates into acid phosphates, is a rise in the acidity of the urine, which I have just pointed out that the nitrites produce; and as the normal phosphate of sodium is a good solvent of uric acid while the acid phosphate is not a solvent at all (see *Medico-Chirurgical Transactions*, vol. lxxii., p. 399), the blood becomes, as a result

of this action of the nitrites, a bad solvent of uric acid and ceases to hold it in solution, and as a result of this the arterioles will be relaxed and arterial tension reduced.

It seems probable, then, that the action of the nitrites on arterial tension is the resultant of two forces; first of all, of the muscular depressant action weakening the muscle fibre in the heart and the vessel walls generally, an action similar to that of tobacco, lobelia, and other depresso-motors (see *Brain*, Spring and Summer Number, 1893, p. 245); and second, of the general relaxation of arterioles which all substances produce which clear the blood of uric acid.

Sir A. Garrod tells us,[1] how he found uric acid in normal blood, and an excess of it in that same fluid, and in the serum of a blister in gout, and the same in lead poisoning;[2] and he there also shows that lead given medicinally diminishes the excretion of uric acid in the urine; and he remarks[3]—"It would appear, therefore, that in individuals impregnated with lead the blood becomes loaded with uric acid, not from its increased formation, but from its imperfect excretion."

This is in absolute and complete accord with my results,[4] and I should apply the same reasoning not to lead only, but to all substances that diminish the excretion of uric acid in the urine; and for my part I have not met with any evidence that there is, or ever has been, an excess of uric acid in the blood due to increased formation, *i.e.*. above the relation to urea of 1 to 33. I believe that for every 33 grs. of urea that are formed in the body, 1 gr. of uric acid is also regularly and punctually formed, but no more. The 33 grs. of soluble urea are excreted with practically absolute certainty; but the insoluble uric acid, though in much smaller quantity, is very apt indeed, from various causes—some of which I shall go into later—to lag behind and be retained in the body.

We shall see also later on, with reference to the above quotation from Sir A. Garrod, that the uric acid is probably not in excess in the blood at the time when under the influence of lead it is diminished in the urine, but it subsequently appears in

[1] "Gout and Rheumatic Gout," 3rd edit., p. 84, *et seq.*
[2] Ibid., p. 240.
[3] Ibid., p. 243.
[4] See *Med. Chir. Trans.*, vol. lxxi., p. 284.

excess in the blood when that which has been held back by the lead is got into solution by alkalies or other solvents in the blood; but as soon as it is in excess in the blood it begins also to pass in excess in the urine.

My investigations, I believe, prove absolutely that an excess of uric acid in the urine above the relation to urea of 1 to 33 comes from an excess in the blood, and that when the uric acid in the urine is diminished below that relation (say 1 to 45) there is little or none in the blood, because every particle that gets into it from the kidney by the renal vein is at once caught up, so to speak, and stored in the liver, spleen, and other tissues.

According to Sir A. Garrod's theory, the antecedent elements of uric acid come probably from the liver to the kidney, and are there formed into urate of ammonium.

By far the largest part of the urate thus formed (say for the sake of a definite quantity nine-tenths) passes at once down the ureter and leaves the body; but the remaining one-tenth may, under certain conditions, pass, according to Sir A. Garrod, into the general circulation through the renal vein; and when there it is attracted differently by different organs, being liable to retention in certain organs which are less alkaline than the blood, and therefore less able to hold it in solution.

It is this residue of uric acid plus that which is directly introduced preformed in food which, according to my interpretation of my results by the light of Sir A. Garrod's hypothesis, furnishes all the uric acid of pathology. If the whole of the urate formed in the body had passed down the ureter as soon as formed, there would have been much less trouble, and to bring about the complete excretion of all that is formed as well as to keep down the quantity introduced, must be the aim of all treatment.

It seems extremely probable that the alkalinity of the kidney structure determines to some extent how much of the urate formed in it shall be at once excreted, and how much shall be temporarily kept back with a chance of eventual passage into the general circulation.

Possibly the pathological urate deposits found in the kidney after death are mere exaggerations of the normal retention which constantly occurs to some extent during life.

To render my meaning clearer, I shall now speak of definite quantities. If a man forms, as my results render it probable

that he does, 1 gr. of uric acid for 33 grs. of urea, let us suppose that he forms in twenty-four hours 12 grs. of uric acid and 396 grs. of urea.

The whole of the urea and 10.8 grs. of uric acid are excreted, giving a relation in the urine of 1 of uric acid to 36 of urea; and 1.2 gr. of uric acid is held back in the kidney, passing gradually into the general circulation.

Once in the general circulation the urate is rendered insoluble and kept back in certain tissues (according to Sir A. Garrod, the liver, the spleen, and the joints and fibrous tissues), because of their relatively diminished alkalinity and consequent deficient power of holding urates in solution.

Next day let us suppose that again 396 grs. of urea are formed and excreted, but this time uric acid is in excess of its normal relation to urea, say 1 to 30; *i.e.*, 13.2 grs. are excreted.

But according to our hypothesis only 12 grs. were formed, and therefore 1.2 gr. must have come from somewhere else, even supposing that all the uric acid formed in the kidney on this day passed direct down the ureter. It is now, of course, evident that the amount of uric acid held back and retained on the previous day furnishes just what is required for the excess in excretion of this day, and thus the excretion of uric acid, but not its formation, fluctuates from day to day.

We can now explain completely why the excretion of uric acid is large during the "alkaline tide" of the morning, and small during the acid tide of the night hours. It is a simple question of solubility in the blood.

Further, by giving alkalies the excretion can (as I have long pointed out)[1] be at any time increased, or by giving acids diminished.

But if the stores in the liver, spleen, and joints have been swept out by the repeated exhibition of solvents, then there is no drug which will cause a plus excretion of uric acid till there has been again some retention and accumulation in these structures.

These facts account completely for all the conditions in which an excess of uric acid is met with in the body; and failure of

[1] See *Journal of Physiology*, vol. viii., p. 216; and *Brit. Med. Jour.*, 1890, vol. xii., p. 124.

excretion will soon keep back as much as is ever found in the body before or after death.

On the other hand, the theories of excessive formation (*i.e.*, formation of uric acid in excess of the normal relation to urea, about 1 to 33) or of deficient oxidation are at once incompatible with the facts I have brought forward, and unnecessary for the explanation of the phenomena of disease.

Sir A. Garrod has also pointed out[1] that there is little or no uric acid in the blood in acute rheumatism, and he proceeds to draw the conclusion that this disease is not due to uric acid. I have given elsewhere[2] my reasons for thinking that this conclusion may require some revision, and I shall have something to say about it further on. My facts are in complete accord with those of Sir A. Garrod; it is only regarding the conclusion to be drawn from them that I venture to differ from him.

One further fact about uric acid is, I believe, mentioned in all text-books of physiology, viz., that it is found as a practially constant constituent of the spleen pulp after death.

It is interesting to note that (as I have several cases to show) uric acid is nearly always present in great excess in the urine in cases of enlarged spleen, as in splenic leucocythemia, and it has been shown by others to be in excess in the blood in this condition.[3]

In several cases of this kind I examined the urine for eight or ten consecutive days, the whole excretion being saved; and in these, over the whole period, the average relation of uric acid to urea in the urine was 1—12 or 1—14. It is little wonder, then, that under these conditions an excess of uric acid should have been found in the blood; the excess in the urine being, as I have said, the index of this.

It may be remembered also that I have shown that there is generally an excess of uric acid in the urine excreted during an epileptic fit. Sir A. Garrod found excess of uric acid in blood drawn during an epileptic fit, and has pointed out the alternation between gout and epilepsy—a fact which my results and conclusions completely explain.

[1] Reynold's "System of Medicine," 1st edit., vol. i., p. 897.

[2] *Med. Chir. Trans.*, vol. lxxiii., "Salicin compared with Salicylate of Soda," &c.

[3] See Salkowski und Leube, *Die Lehre vom Harn*, p. 88.

Then there is Sir A. Garrod's explanation of the presence of uric acid in the spleen, which I have so often quoted,[1] and which serves so admirably to explain many of my results.

In his Lumleian Lectures,[2] he suggests that when uric acid is present in the blood, it is attracted differently by different organs, and that the spleen being perhaps less alkaline than the blood, the uric acid becomes less soluble in it, and more easily retained. Such a suggestion will, as I have said, explain nearly all my results, and they in their turn will go, I think, a long way towards proving that what Sir A. Garrod suggests does actually take place.

I pointed out in the *Journal of Physiology* (previous reference) that it is quite easy by giving an acid to diminish the excretion of uric acid in the urine; and as the amount of uric acid so kept back can be brought out and excreted later on by giving an alkali or salicylate or other solvent, it is evident that the uric acid is not altered or destroyed, but only kept back or retained by the acid.

Now the absorption of an acid raises the acidity of the urine, and diminishes in passing the alkalinity of the blood and tissue fluids: and it follows from what has been said above that any diminution of the alkalinity of the blood and tissue fluids will diminish the amount of uric acid they can hold in solution.

And if the liver, spleen, and joints are less alkaline, as Sir A. Garrod has pointed out, than other tissues, any uric acid coming to them in the blood stream is rendered, as Sir A. Garrod puts it, "less soluble and more easily retained," and we can at once explain why these tissues are frequently found after death to contain considerable quantities of uric acid.

In order to estimate the amount of uric acid in the blood and tissues, I first of all made a water-extract of them by a process described by Salkowski and Leube,[3] and then having evaporated and cleared my solution, I applied Haycraft's process to it, just as in the case of urine (see chapter xviii.).

In specimens of human blood obtained during life, I found quantities of uric acid ranging from .03 per cent. in a case of cerebral hæmorrhage to .0006 per cent. in a case of cellulitis, the

[1] See *Journal of Physiology*, vol. viii., p. 214.
[2] *Brit. Med. Jour.*, vol. i., 1883, p. 549.
[3] *Die Lehre vom Harn*, p. 94.

blood flowing from incisions into the inflamed tissue. In the blood of a fatal hæmoptysis in a case of fibroid phthisis, the patient being at the time on salicylate of soda, I found .0065 per cent. of uric acid, and having plenty of blood to work on in this case, I was able to estimate the quantity more accurately than is generally possible with small samples.

With regard to the very small quantity of urate in the blood from incisions in an arm affected with cellulitis, Sir A. Garrod, it may be remembered, has pointed out ("Gout and Rheumatic Gout," pp. 187 and 274), that there is no urate in the fluid of a blister or in blood drawn directly over the inflamed joint in gout, and suggests as an explanation that inflammation destroys uric acid.

My facts are in complete accord with his; but I think the explanation is that local inflammation means local reduction of alkalinity, so that all urate coming to that part is rendered insoluble and retained, and the blood or serum which have passed through the inflamed part are practically cleared of uric acid. So in acute rheumatism the urate is in the joints and the blood is cleared of it; but in gout (a more local disease) only that part of the blood which has passed through the inflamed area is cleared of urate.

In specimens of human blood obtained after death from the heart cavities, it seemed to me that where the joints contained urates there was more in the blood than when they contained none—thus eleven cases with urate deposits gave .03184 per cent. of uric acid in the blood, and eleven cases in which there were no urates gave an average of .02255 per cent.

Then I noticed that in the blood of cases dying of pneumonia there was generally a great excess of uric acid, and five cases of this kind gave an average of .03742 per cent.; but in a case of pneumonia and delirium tremens the blood obtained by venesection, while the temperature was 102°, only contained .0006 per cent., and this fact enables us at once to explain the great excess met with in the blood of these cases after death.

During the acute onset and high fever of the first two or three days of a pneumonia, there is a great rise of acidity, or what amounts to the same thing, a fall in the alkalinity of the blood and tissue fluids, and this drives all the uric acid out of the blood, and retains it in considerable quantity, for the reasons previously

given, in the kidney, liver, spleen, and possibly the joints and other tissues. There it goes, and there it remains so long as the fever is able to keep down the alkalinity of the blood and tissue fluids: but when the temperature falls, the alkalinity of these fluids quickly rises, and the retained uric acid is soon got again into solution, thus coming to be in excess in the blood, and passing from it in excess in the urine; the excess of uric acid in the blood accounting for the headache and mental depression and suicide, with slow high tension pulse and subnormal temperature, which are so common in convalescence from acute febrile diseases.

If, however, the patient dies, precisely the same thing occurs. For some hours before death there is great failure of nutritive processes; and even if the fever keeps up, the alkalinity of the blood and fluids may rise, owing to the failure of nutrition and of respiration. Hence uric acid is dissolved out from its places of deposit, and is in excess in the blood at the time of death, this excess being, as will now be understood, the direct result of its expulsion from the blood and retention in certain organs during the diminished alkalinity of the acute fever.

Then again, cases in which at the time of death the temperature was high and rising, as in meningitis, yield generally only a small amount of uric acid in the blood; but there are several exceptions to this rule, due probably to the fact above mentioned, that in spite of high temperature the alkalinity of the blood and fluids may be rising, owing to general failure of nutrition; and in one case of pyæmia with embolic hemiplegia I got quite a large amount (.05426 per cent.) in the blood, in spite of a temperature rising to 104° at the time of death; and in another case of cerebral lesion about the same amount. With reference to cases of this kind, I would suggest that the cerebral changes (softening) in connection with the hemiplegia would cause the passage through the blood of a large amount of phosphates;[1] and that, as I have pointed out,[2] certain phosphates of soda, potash, and ammonia are powerful solvents of uric acid, and greatly increase its excretion, and no doubt its quantity in the blood for the time being.

Two cases, in which the blood contained .01243 and .05880 per cent., had .06384 and .08668 per cent. in the spleen respectively, the relative excess in the spleen being in accord, as

[1] *Zuelzer. Semiologie des Harns*, p. 89; and *Brain*, vol. ix., p. 364.

[2] *Med. Chir. Trans.*, vol. lxxii.

previously mentioned, with all that is already known on the subject.

Nine cases of morbus cordis gave an average of .03350 per cent. in the blood after death.

For the rest, my results show that the blood after death generally contains some little uric acid, though the amount is subject to considerable variation: the largest quantity met with being .0744 per cent. in a case of pneumonia, and the smallest .01008 per cent. in a case of meningitis.

Eight specimens of liver yielded an average of .05928 per cent., and the liver of a six months' fœtus that did not survive its birth yielded .003 per cent.

Five specimens of spleen yielded an average of .06412 per cent., or slightly more than the liver.

Nine specimens of kidney yielded an average of .0513 per cent., that is, less than either the liver or spleen. One kidney (not included in the above), from a child of thirteen days old, which contained well-marked uric acid infarcts, yielded the very large quantity of .23 per cent., or more than four times as much as the above specimens. My best thanks are due to my colleague, Dr. S. W. Wheaton, who kindly placed this most interesting specimen at my disposal. He informs me that the uric acid of these infarcts, which were plainly visible in the medulla of the kidney, was seen under the microscope to be both in the tubules and in the connective tissue round them, which, according to authorities on the subject, is generally the case (see Zeigler, *Pathologische Anatomie*, vol. ii., p. 333). The kidney of the above-mentioned six months' fœtus contained .002 per cent.

A piece of human psoas muscle contained apparently .028 per cent. It may also be interesting to mention here that half-a-pound of beef-steak yielded .019 per cent., and that I found the equivalent of .697 per cent. in some meat juice, and of .883 per cent. in some meat extract.

In a case, in which the blood from the heart had .06904 per cent. (a very large quantity), the urine drawn from the bladder gave a relation of uric acid to urea of 1 to 9.4, a very great excess in the urine also. In a case with .02384 per cent. in blood, the relation in the urine was 1 to 27; *i.e.*, much less in both. In another case there was .03024 per cent. in blood, and relation in urine 1 to 29. And in another, .03914 per cent. in blood, and

urine relation 1 to 10; *i.e.*, a considerably greater excess in the urine than in the blood.

And in another case .06888 per cent. in the blood, and a relation of uric acid to urea in the urine found in the bladder of 1 to 18, and the percentage of uric acid in the urine was .03696. The liver in this case contained .088 per cent. The amount in the spleen was not estimated, but no doubt, as in other cases, it contained nearly as large an amount as the liver. I would remark, in passing, that these facts seem to me to be strongly in favour of my argument that the excess in the urine is an overflow from the excess in the blood, and that the excess in the blood again is due to its dissolving out and taking up some of the stores in the liver and spleen.

A similar explanation can be given of the greater quantity of uric acid in the blood of cases which have urates in their joints; here the blood has obviously an additional storehouse from which supplies of uric acid can be drawn. And in cases of chronic wasting disease, it is easy to demonstrate that it does draw on it; that for weeks together there is, as I have observed, an excessive excretion of uric acid in the urine, and after death erosion of joints is found, but all or nearly all the urate has been dissolved out of them.

These results show that when there is excess in the blood there is also excess in the urine; but we must not, I think, press the matter more closely than this, or we shall get into difficulty and error.

We must remember that the urine found in the bladder after death is the excretion possibly of several hours during which the amount of uric acid in the blood fluctuated considerably, so that nothing more than a general rough relation between the two can be expected.

I have also made a few examinations of the blood and organs of animals.

Dog killed after operation under chloroform: blood contained .00168 per cent. That of another dog .00336 per cent., and the urine of this dog obtained at the time of death gave a relation of uric acid to urea 1 to 85, which is a large amount of uric acid for a dog.

The urine of a cat gave a uric acid urea relation of 1 to 110.

The blood of several other dogs contained very small traces,

about .00126 per cent.; their livers from .04 to .02 per cent., and their urine at the time of death gave uric acid urea relation of 1 to 136 to 1 to 144.

I then tried to work on the urine of a single animal (dog) to collect it day after day, and to try and alter the uric acid urea relations by diet and drugs.

A bitch, weighing 11 lbs., was kept in the ordinary form of cage for collecting the urine, and was fed on 6.6 oz. boiled horse, 5 oz. milk, and 5 oz. of water.

The urine was passed at very irregular intervals, but the uric acid urea relation was 1 to 87 on the first day, and 1 to 165 on the fifth and last day of the above meat diet; urea being 25 grs. per lb. So that it rather appeared that the meat diet in the dog, as in man, diminishes the excretion of uric acid at first.

The animal was then put on a diet of porridge O. i., and milk O. iss., which, however, it took very badly; on this urea fell very greatly down to 13, and eventually even to 5 and 6 grs. to the lb., and uric acid increased relatively, being 1 to 146, 1 to 110, and 1 to 98.

On the last day of this experiment I gave hyposulphite of soda in the milk with the object of diminishing the uric acid, and apparently with some success, as the relation altered to 1 to 143.

The animal, which now weighed 13 lbs. (an increase of 2 lbs.) was killed, and the blood, liver and kidneys examined.

The blood contained .0003 per cent.
,, liver ,, .0287 ,,
,, kidneys ,, .0460 ,,

The very small quantity in the blood was in accordance with the diminution in the urine, which again was probably due to the drug given.

In other dogs I attempted to increase the uric acid in the blood and urine by giving salicylate of soda, but this failed completely. There was practically no uric acid in the blood of either of the two animals thus treated, nor was there any increase of uric acid in the urine, the relation being in this latter fluid 1 to 140 to 1 to 150. Both urines gave a strong salicin reaction with perchloride of iron, so that the drug was plentifully absorbed and excreted.

Now, I think that this is a very interesting fact, that salicylate of soda, which has such a great power over the excretion of uric acid in man, should produce absolutely no effect on it in dogs.

I think, however, that I can see my way to some explanation of the fact, as in all that I have written about the action of salicylate of soda in man, I have always been careful to point out that acids aid, and alkalies hinder, its solvent action on urates (see p. 19). Now, strange as it may seem, the acidity of dogs is very low indeed; and the bitch that I fed on horse-flesh, though excreting 25 grs. of urea per lb., only excreted acid to the equivalent of 1 grain of oxalic acid for 16 to 17, or even 18 grs. of urea, the acidity urea relation being 1 to 18; but in man, as I have shown in my own case, it is 1 to 6.1; so that this dog (a carnivore), excreted only one-third of the acid per grain of urea that we do; probably, therefore, its blood was far more alkaline than that of a man on the same diet, and hence the salicylate failed to affect the uric acid as it does in man.

With regard to the above relation of acidity to urea, Dr. A. Auerbach has pointed out (Virchow's *Archiv.*, 98-3, p. 512) that no amount of acid that can be given will render the blood of carnivora acid, as they form ammonia to neutralise the acid, and no doubt something of the sort accounts for the very low acidity in the dog above mentioned.

In two monkeys, the organs of which were very kindly placed at my disposal by my colleague, Dr. H. H. Tooth, I found in the blood about .00441 per cent., in the liver .060 per cent., in the kidneys .050 per cent., and in the muscles of the back .017 per cent. of uric acid.

Alongside of my results it may be interesting to mention those of a well-known author, Professor R. v. Jaksch, of Prague, who in a paper "Ueber uricacidæmie" (*Deutsch. Med. Wochenschrift*, Aug., 1890, p. 741), gives the results of his investigations into the uric acid in the blood, together with an explanation of the causes that tend to increase its quantity.

His facts in the main are in accord with my own; but his conclusions from them are based on what I believe to be a completely erroneous theory, that all increase of uric acid in the blood is due to deficient oxidation, and not, as I have for some years been endeavouring to show, to a retention of it in the body, leading to subsequent increased excretion, the increase passing through the blood on its way to the kidneys.

Now, Professor v. Jaksch relates that he found no demonstrable uric acid in the blood of nine healthy individuals, and the

same in cases of tabes, multiple sclerosis, polyneuritis, and cerebral tumour.

I should have expected that if there was any wasting in the diseases mentioned there would have been some uric acid in the blood, but as all the facts are not given, it is impossible to draw any definite conclusion.

To reason from the results in healthy subjects, it would be necessary to state the time of day at which the blood was drawn; for my researches make it extremely probable that there is some appreciable amount of uric acid in the blood of every one for an hour or two during the "alkaline tide" of the morning, and that the excess in the urine commonly met with at this time is an overflow from some excess in the blood; and, as I have elsewhere pointed out, the mental condition and the rate and tension of the pulse often point to excess of uric acid in the blood in the "alkaline tide."

Again, in nine cases of typhus, Professor v. Jaksch found no uric acid in the blood; but it was present in one case after the fever had gone. Similarly in intermittent fever there was no uric acid during the fever, but when the temperature fell uric-acidæmia supervened.

This, it will be noticed, is in complete accord with my results and reasoning. When there was fever the alkalinity of the blood was diminished, the uric acid became less soluble in it, and was retained in the liver, spleen, joints, &c. The enlargement of the spleen in malarial fevers has an interesting relation, as I shall have to point out at some future time, to the amount of uric acid that can be retained in the body in this disease, and in other diseases in which this organ is enlarged. I have found the spleen, as above shown, to contain about .3 grs. to the oz.; obviously a spleen weighing 6 to 8 lbs. would contain 28 to 38 grs., and if this organ is alternately filled up and emptied in the alternations of fever and remissions, we shall be able to account for all the uric acid which is so often found in excess in some part of the body in these cases. Again, if we reflect that the holding back or retention of little more than 1 gr. a day (and it is easy on any given day to produce a retention to this extent with drugs) will furnish 1 oz. of uric acid in a year, we shall be at no loss to account for all that is ever met with in the body after death, whether in the joints, viscera, and tissues, or in the urinary passages in the form of calculi.

On the fall of temperature the alkalinity of the blood was increased, and it dissolved out and removed the uric acid from its places of deposit; if the urine had been examined at the same time, corresponding changes in the quantity of uric acid excreted would have been observed, and as I have elsewhere pointed out, the amount of urinary water and the rate and tension of the pulse would show concomitant alterations corresponding to the effects of the uric acid on the arterioles.

In diseases of the liver, intestines and stomach, there was only uricacidæmia when they went along with anæmia. I should be inclined to read for anæmia wasting and debility, with their result a fall in the excretion of urea and acid, and consequent fall in the acidity of the urine and increase in the alkalinity of the blood. Among heart diseases he observes that those had most uric acid in the blood in which the disease caused most cyanosis.

Again he often found uric acid in the blood in diseases of the lungs and pluræ, emphysema and exudations.

He found it constantly present and in considerable quantity in five cases of pneumonia even during the febrile stage.

The explanation of these results in pneumonia which appear to be in opposition to my result will be gone into presently. The blood, in the single case of this disease I was able to examine, was drawn early in the acute stage of the disease, and it must be remembered that in my results with *post-mortem* blood I found an extremely large amount of uric acid in the blood of pneumonia cases.

None in six cases of rheumatic fever.

A very considerable quantity in kidney diseases of different forms, ten cases.

From these results he deduces the general statement that the blood contains much uric acid in all cases of primary and secondary anæmia;

That uric acid is present in the blood in considerable quantities in other diseases besides gout;

That uric acid does not take part in the acid intoxication of fever, since fever is unfavourable to the presence of uric acid in the blood;

That in dyspnœa and cyanosis the more the blood is overloaded with carbonic acid, the more uric acid it contains.

Hence in pneumonia you may get uricacidæmia in spite of the fever.

And lastly, he concludes that it is plus in nephritis and anæmia, because the red cells are unable to further oxidise the uric acid, and hence anything that interferes with the oxygen-carrying power of the red cells causes excess of uric acid in the blood.

This sounds on the face of it a very plausible conclusion, but my researches on the excretion of uric acid throw, I think, considerable doubt on its validity.

It has long been known that the excretion of uric acid is large in the morning when the acidity of the urine is low, in what Sir W. Roberts has named the "alkaline tide."

This has, I think, been generally regarded as due to a plus formation of uric acid during these hours; but I have shown that the excretion of uric acid, both in these hours and at other times of the day, can be altered in either direction. The natural plus excretion of the "alkaline tide" can either be increased very considerably, or diminished to a corresponding extent. If it is required to increase it, this can be done by first retaining a little uric acid in the body by acids given on the previous day, and then increasing the alkalinity next morning with a dose of alkali. If it is required to diminish it, this can be done directly by giving an acid to counteract the alkali of the "alkaline tide;" or more powerfully still, by removing all the most easily available uric acid stores on the previous day by giving a powerful solvent, as salicylate of soda, when the "alkaline tide" next morning will have nothing to act upon, and there will be no plus excretion of uric acid. I have given instances of all these results before, and any one who will take the trouble to give a few drugs and watch the results, may easily convince himself that the excretion of uric acid can be varied at pleasure in either direction.

It may be of interest if, in illustration of what I have been saying, I refer again to fig. 4, p. 20. From this it may be seen that a dose of 15 grs. of the salicylate, taken three times a day for five days, produced on the first day it was taken a very large excretion of uric acid. Next day, the drug being continued as before, it fell down close to the urea again; then on the two following days (4 and 5 in the figure) it rose a little, but to

nothing approaching the height of its rise on the first day (Day 2 of figure). On Day 6, the last day of salicylate, it came still nearer the urea; and on Day 7, when salicylate was left off, it fell very far below the urea, and remained there, as my curves not given in the figure) show, for the three following days.

All curves of uric acid excretion under salicylate show practically the same thing, and the same is seen in the excretion curve of acute rheumatism treated by this drug (see fig. 35), only that the quantities are greater. In all, the excretion reaches its highest point on the first or second day, and the same height is never again attained, however long the drug is continued. On the contrary, the excretion shows a tendency, with a few oscillations, to come down to the level of the urea and remain there; and if the drug is now stopped it at once falls far below the urea, and remains there for several days.

My explanation of these results is, that on the first day it is given the salicylate meets with a considerable amount of uric acid in the joints, liver, spleen, &c., on which it is easily able to act; that as it gets this into solution and passes the greater part of it into the urine, it never on any subsequent day meets with so much uric acid on which it can act, hence the curve never rises so high again. On subsequent days a little here and there comes within its range of action, but each day there is less and less left, so that the curve approaches the urea that is the level of formation.

As soon as the drug is withdrawn there is at once a retention of uric acid (Day 7), replacing to some extent what has been removed from the organs and tissues by the solvent.

If on Day 2 an alkali had been given in place of the salicylate, it would have produced a plus excretion of uric acid; but the same dose of alkali given on Day 7 would have quite failed to raise the uric acid above the urea; the more powerful solvent salicylate has now removed so much uric acid that the alkali has nothing to act upon. It will now be understood that by giving drugs in this manner, and watching their effects from day to day, or, if need be, from hour to hour, it is no very difficult matter to alter the excretion of uric acid in any required direction.

The plus excretion of the "alkaline tide" is thus seen to be a single instance of a general rule which may be thus stated. All substances which increase the solubility of uric acid increase its

excretion (provided there is some uric acid in the body for them to act upon); and conversely, all substances which diminish the solubility of uric acid diminish its excretion, and cause it to be kept back and retained in the body. If the normal plus excretion of uric acid in the "alkaline tide" was due to plus formation, why should the previous removal of uric acid diminish it, or why should the previous storing up of uric acid increase it?

I have given above my reasons for believing that every plus excretion of uric acid in the urine is simply the overflow from an excess of this substance in the blood, and that when there is a diminished excretion in the urine there is none, or almost none, in the blood. In other words, that the amount of uric acid in the urine in relation to the urea is the index of the amount in the blood, and that in altering the amount in the excretion we of necessity alter at the same time the amount in the circulating fluid.

The results published by Professor v. Jaksch will presently be seen to be simple instances of the action of the law of solubilities above stated.

From my point of view I can show that alkalies (except lithia), phosphate of soda, and compounds of salicylic acid, increase the excretion of uric acid in the urine, and for a time also increase the amount of it in the blood. Conversely acids, iron, lead, and lithia, diminish the solubility of uric acid, diminish its excretion in the urine and the amount of it in the blood. That acids, iron and lead interfere with the solubility of uric acid is well known, and lithia, as I have pointed out elsewhere,[1] though said to be a beautiful solvent of uric acid in a test tube, yet when given to the human subject by mouth never reaches the uric acid at all, because it at once forms an insoluble compound with the phosphate of soda in the blood, thus removing from that fluid one of the natural solvents of uric acid, and diminishing its power of holding uric acid in solution; and in accordance with this, as I have pointed out, it diminishes the excretion of uric acid in the urine and the amount contained in the blood, and as a result of this it has the same effect on the rate and tension of the pulse, the flow of urine, and the circulation of the brain (as evidenced by the mental condition); that acids, iron, and lead have, though

[1] *Med. Chir. Trans.*, vol. lxxi., p. 287.

acids raise the acidity of the urine and diminish the alkalinity of the blood, and lithia lowers the acidity of the urine and increases the alkalinity of the blood; thus clearly showing that the pulse rate and tension and the circulation in the various organs mentioned are not directly affected by the drugs used, but only indirectly through their effects on the solubility of uric acid and the amount of this substance which the blood can hold in solution.

Under ordinary circumstances a dose of potash or soda will increase the excretion of uric acid in the urine, and will also increase the amount of uric acid in the blood; as the result of this, it will slow the pulse, raise the tension, and produce mental depression and scanty urine from its effect on the circulation of the brain and kidney respectively; but if all the available uric acid has been cleared out of the body by giving a salicylate for two or three days beforehand (see fig. 4), then a dose of soda or potash will produce no plus excretion of uric acid in the urine and no excess of it in the blood; and in accordance with this, none of the above-mentioned vascular phenomena will make their appearance, and the circulation in the brain and kidney will go on unhindered; thus proving beyond all doubt, that these vascular phenomena are due, as I have previously pointed out, not to the direct action of the drugs used, not to the greater or less alkalinity of the blood *per se*, but to the larger or smaller amount of uric acid which it is able to hold in solution.

In several papers I have mentioned the very interesting parallel between my results on the human subject and the results obtained by Drs. Roy and Sherrington in animals by the injection of acids and alkalies into their veins.

I have pointed out that when an alkali is given and increases the amount of uric acid in the blood, it contracts the arterioles generally and raises the tension of the pulse: and as the result of this we get, as regards the kidney, scanty urine, and as regards the brain, deficient circulation and mental depression. Now Drs. Roy and Sherrington point out[1] that alkalies injected into a vein diminish the volume of the brain, *i.e.*, I suppose, the amount of blood circulating in it.

Conversely I have shown that when acids are given and clear the blood of uric acid, the vessels generally are relaxed and the

[1] *Journal of Physiology*, vol. xi.

pulse tension reduced; the urine becomes copious, and the mental condition one of happiness and well-being. Drs. Roy and Sherrington show that injection of acids increases the volume of the brain.

I have just given my reasons for thinking that these vascular effects are not due to the direct action of the drugs, but are secondary to their influence on the amount of uric acid in the blood.

It may be urged that the results obtained by Drs. Roy and Sherrington follow too quickly on the injection of the acid to allow of their being due to the altered amount of uric acid in the blood. I do not, however, think much of this objection, because in the human subject the results are practically instantaneous if we allow for the time which a dose takes to be absorbed from the stomach in sufficient quantity to affect the reaction of the blood. It is no uncommon experience to get some pricking pains in the joints a very few minutes after swallowing a dose of acid, and the urine of the fifteen minutes following the dose may show a distinct diminution in the uric acid excreted.

The process should probably be regarded as a chemical reaction, and the precipitation of uric acid looked upon as occurring the moment an acid is added to its solution. In forty-five minutes I have often completely cleared the blood of uric acid, curing a uric acid headache, and greatly diminishing the excretion in the urine; but long before this very distinct results are evident, and if acids could be injected into a vein, and blood drawn before and after the injection, I have no reason to doubt that a practically instantaneous change in the amount of uric acid could be demonstrated.

What seems to me a more serious objection to my explanation of Drs. Roy and Sherrington's results is the very small amount of uric acid contained in the blood of dogs (the animals used for the most part in their experiments). Now dogs and cats have, as is well known, much less uric acid in their urine than man has; and the relation I have found for them is about 1 of uric acid to 100 of urea, *i.e.*, they excrete only about one-third of the uric acid per grain of urea that we do. Similarly they have much less in their liver also, as .15 to .16 gr. to 1 oz., as compared with .3 to .4 gr. to 1 oz. in man. See p. 51.

This, however, does not show that their blood contains no uric acid—working on large quantities it could certainly be found—nor does it show that the results of Drs. Roy and Sherrington are not due to uric acid, as we have abundant evidence that very minute quantities of chemical substances will produce physiological results, and it is quite possible that the arterioles of these animals, whose blood contains so little uric acid, are more sensitive to it than those of man, whose blood contains more.

I think that the connection traced by Professor v. Jaksch between deficient oxidation and excess of uric acid in the blood is quite correct as regards the facts, only the explanation is probably a little different from that which he has given.

Dr. Peiper, whom v. Jaksch quotes, points out that the alkalinity of the blood is diminished in all fevers, except when they are complicated by dyspnœa and cyanosis.[1]

Now this is a most important exception, and on further investigation it will, I think, be seen that it furnishes us with an easy explanation of most of Professor v. Jaksch's facts.

It may be worth while to stop for a moment and enquire why dyspnœa and cyanosis, that is, deficient oxidation, should prevent the diminution of the alkalinity of the blood which commonly takes place in fever.

We have not very far to look for an explanation, for the word oxygen itself supplies one to hand, as its derivation, given in every work on chemistry, *οξυς*, acid, and *γενναω*, I produce, at once furnishes a clue.

It is extremely probable, one might almost say certain, that oxygen in the human body acts just as in the chemical laboratory, and when it oxidises certain substances produces certain compounds of an acid nature, and that form of motion which we call heat.

I know as a fact that when certain compounds of sulphur are given by mouth, they themselves having a neutral reaction, there is soon seen a very marked rise in the acidity of the urine, as if a very strong dose of acid had been given, and this rise goes on for some little time. Now, it seems to me that there can be scarcely any room for doubt that this is due to the oxidation of the sulphur with the formation of some acid.

[1] Virchow's *Archiv.*, June, 1889, p. 337.

And it is extremely probable that in the ordinary metabolism of the human body exactly the same thing occurs, that oxygen combines with certain elements in the food or tissues to form as in the laboratory heat and acids; in fever the same processes are carried to excess, and we have as their result a rise of body temperature and an increased formation of acids causing a rise in the acidity of the urine and a fall in the alkalinity of the blood. (See also chapter iv.)

But if oxygen is deficient, if there is dyspnœa or cyanosis, the chemical changes are interfered with and the temperature does not rise so high, and there is a lessened formation of acid; hence, as pointed out by Dr. Peiper, the alkalinity of the blood is not diminished.

If then, with regard to the amount of uric acid found in the blood by Professor v. Jaksch, we read for deficient oxidation, *deficient formation of acids*, we are at once in a position to explain all his results; as the excess of uric acid which he finds in the blood in all conditions of diminished oxidation can at once be accounted for by my law of solubilities previously stated.

In ordinary fevers the increase of oxidation diminishes the alkalinity of the blood and reduces often to *nil* the amount of uric acid it can hold in solution; hence the results of Sir A. Garrod in acute rheumatism and the concordant results of Professor v. Jaksch and myself in fever and inflammation.

But if there is a deficiency of oxygen the acids are not formed, the alkalinity of the blood is not diminished—it may even be increased; and its solvent power for uric acid being thus undiminished or increased, it at once takes up a large amount in solution, and there is a corresponding increase in the amount passed in the urine.

As I have before also pointed out, precisely the same changes in the amounts of uric acid in the urine and in the blood can be produced at will by giving alkalies and acids respectively.

There is, as I have said before, no reason to believe in the existence of an excessive formation of uric acid, and all fluctuations in excretion can be explained by its simple retention from previous failure of excretion, so that what Sir A. Garrod said about lead (previous quotation) is probably true of all substances that affect the excretion of uric acid in the same way.

Practically, in the human body uric acid is always formed in

a definite proportion to urea, about one grain of uric acid for 33 grains of urea; and I have given above some reasons for this statement. Sir A. Garrod[1] noted this fact, and sought to explain it by suggesting that certain cells in the kidney formed urea, and certain other cells, having a definite numerical relation to them

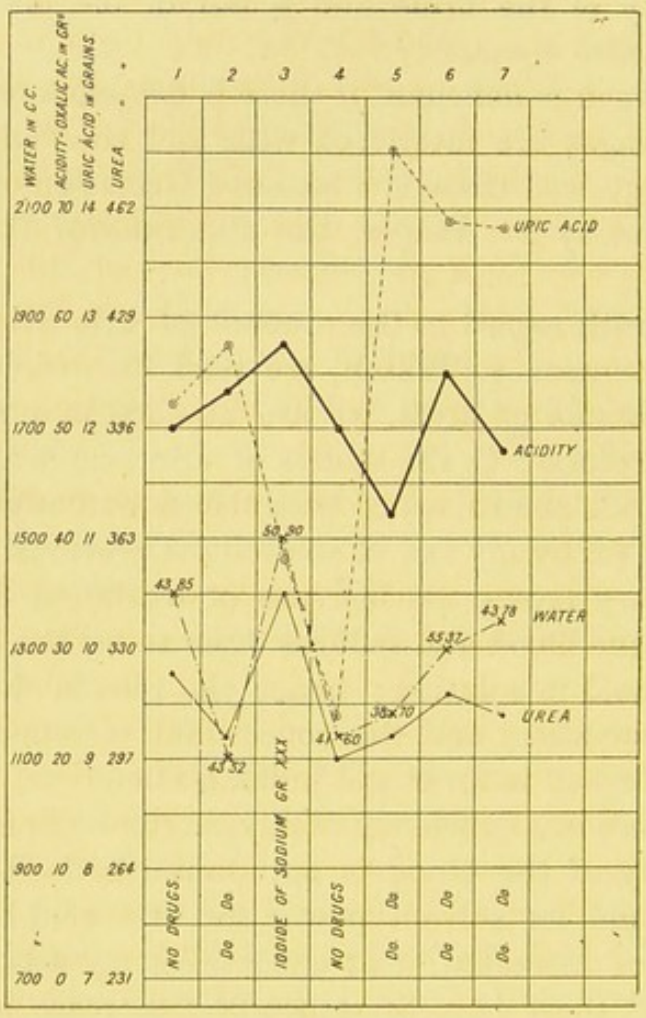

FIG. 14.—RETENTION OF URIC ACID PRODUCED BY IODIDES.

formed uric acid; but I am inclined to believe that a satisfactory chemical explanation of the relative formation of these two substances may yet be forthcoming.

Fig. 14 shows the effect of an iodide on the excretion of uric acid. On Day 1 uric acid is high and on Day 2 it rises still further. On Day 3 gr. x. of iodide of sodium are taken three times and uric acid falls and comes close to urea; and on Day 4,

[1] *Brit. Med. Journ.*, vol. i., 1883, p. 547.

though no more of the iodide is taken, it falls further and remains close to the urea. On the remaining days of the figure no drugs are taken, but on Day 5, the effect of the iodide having now passed off, uric acid rises very high. This constitutes what I have spoken of as the rebound, and makes it probable that the low excretion of urate on Days 3 and 4 was not due to its destruction or elimination in other forms but to its retention in the body, the iodide making the blood for the time being a bad solvent of urates, so that they are retained in the liver, spleen, kidneys and fibrous tissues, and when the effect of the iodide passes off they are again taken up by the blood from these organs and tissues and excreted in excess in the urine. A similar plus excretion of the rebound is seen after all substances which, like iodine, cause retention of uric acid. Those substances on the other hand which cause a plus excretion of uric acid, as alkalies, salicylates, &c., are followed by a great fall in urate excretion the day after they are left off.

On Days 6 and 7 in this figure uric acid remains high and a long way above urea.

Note also that the usual relation of uric acid to acidity is broken through, for urate falls and remains low on the fourth, though acidity has fallen decidedly. On the fifth, however, the effect of the iodide passes off and the fall of acidity allows of a plus excretion of urate; on the sixth acidity rises and urate falls somewhat, so that it has regained its normal relation to acidity.

See also the excretion of water, how it rises to 1,500 cc. on the third with the fall of urate down close to urea. On Day 2 uric acid exceeds the relation to urea of 1—33 by nearly 3½ grs., that is to say, on this day about 3½ grs. of uric acid passed through the blood, the arterioles of the kidney and whole body were contracted by the urate, and hence the urinary water was scanty, only 1,100 cc. On Day 3 the iodide produces its well-known diuresis, and this diuresis, like that of many other drugs which cause retention of uric acid, is due to its clearing uric acid out of the blood. On Day 3 uric acid was above urea by only ¼ of a gr., therefore, only ¼ gr. passed through the blood, the arterioles were everywhere relaxed, the circulation through the kidneys was free and the urinary water ran up to 1,500 cc.

In a paper on "The Iodides and their effects on arterial tension and the excretion of urates," *Transactions of the Royal Medical*

and Chirurgical Society, 1893, I have pointed out that the relaxation of arterioles and the diuresis which the iodides produce are contemporaneous with a diminished excretion of uric acid in the urine, and I have further said that a large number of drugs and disease processes which similarly dimish the excretion of uric acid and clear it out of the blood produce also a relaxation of

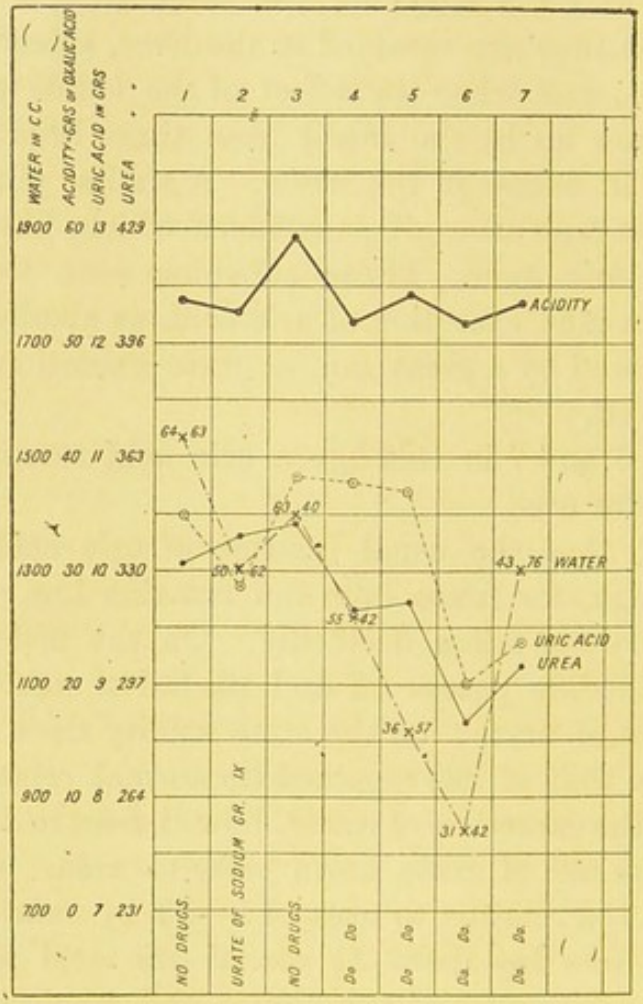

FIG. 15.—EFFECT ON THE EXCRETION OF URIC ACID OF SWALLOWING URATE OF SODIUM.

arterioles and a diuresis, and that arterial tension is influenced, not by the drugs, but by their effects on the solubility of uric acid and the amount of this substance present in the blood. But I must refer my readers to the above mentioned paper for further figures and details of my investigations on the iodides.

Fig. 15 shows the effect of taking urate of sodium (grs. 9) by mouth, and it apparently produces a rise in the excretion of uric

acid, not on the day it was taken, but on the first, second and third day after the dose. Precisely the same thing occurs if uric acid is taken in place of a urate, but in this case there is generally a more marked rise of acidity on the day the dose is taken, and this is accompanied by a rise of urea a retention of uric acid, and more or less diuresis; on one of the following days, however, acidity falls again, and uric acid rises and remains high for several days more or less in proportion to the dose taken.

If, however, acidity runs at a very high level, as in a person who eats much meat and drinks wine, taking uric acid or urates by mouth may apparently produce no effect whatever on the excretion of uric acid; for the excretion of uric acid is dependent on its solubility in the blood, and where the conditions are unfavourable for this solubility it remains in the body instead of passing through the blood into the urine. In this figure it was the fall of acidity on Day 4 that made the plus excretion of urate on this and the following day possible, but had there been no urate introduced this fall in acidity might not have been followed by a rise in its excretion.

If, on the other hand, the blood is kept in a condition to hold uric acid in solution by supplying it with alkalies or salicylates before-hand, the uric acid or urates taken by mouth pass almost at once through the blood into the urine, and by repeating and varying the dose, it is easy to show that the excretion is proportional to the amount ingested. Thus in the *Journal of Physiology* (vol. xv., p. 167) to which I must refer for further figures and details, I have shown that while a given dose of salicylate of soda produced in five days, under ordinary circumstances, an excretion of uric acid which exceeded the relation to urea of 1 to 33 by 11¼ grs., a similar course of salicylate taken on other five days along with 12 grs. of uric acid produced an excretion of 20¼ grs. above the relation to urea of 1—33.

It does not seem to me that there is any reason to doubt that the extra 9 grs. excreted on the latter occasion came from the quantity ingested, and that if the experiment had been continued a day or two longer the whole of the 12 grs. would have been excreted.

Fig. 16 shows the effect of a meat and wine dinner in increasing the excretion of uric acid, for meat contains a considerable percentage of this substance (see table in chapter xvii.), and some

of this passses more or less quickly into the blood and out in the urine.

The dinner is taken on Day 2, and it happened to be preceded and accompanied by a little dyspepsia and headache; this prevented there being much rise of acidity, and there was no rise of urea. The slight rise of acidity was probably directly due to the

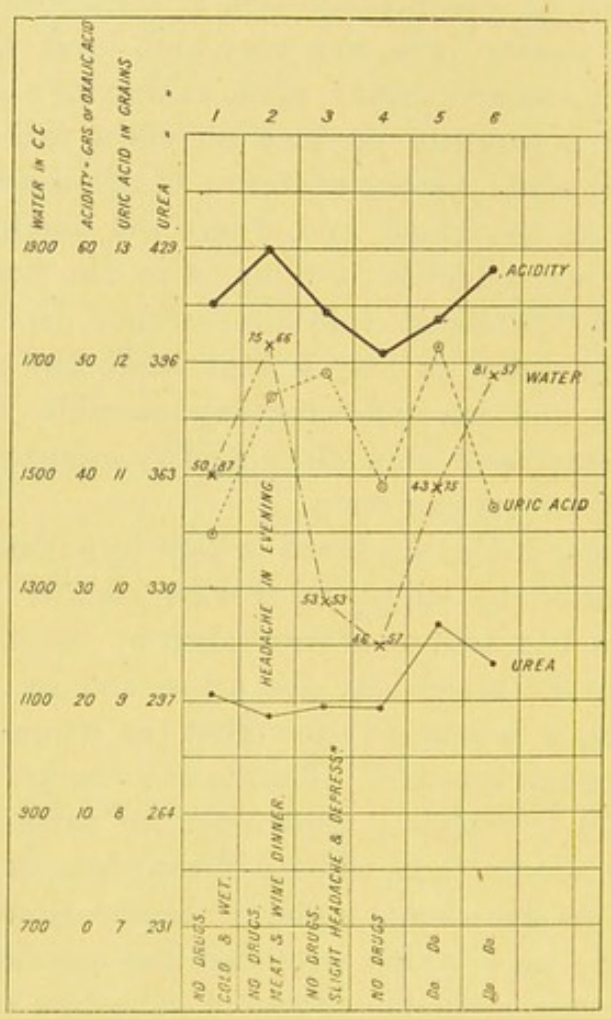

FIG. 16.—EFFECT ON THE EXCRETION OF URIC ACID OF A MEAT AND WINE DINNER.

wine taken, and it was insufficient to interfere with the free excretion of uric acid which accordingly rose. On Day 1 uric acid exceeded urea by $1\frac{1}{2}$ grs.; on Day 2 by $2\frac{3}{4}$ grs., and on Day 3 by rather more than this; on Day 4 it exceeds it by nearly 2 grs., on Day 5 by $2\frac{1}{2}$ grs., and on Day 6 it only exceeds it by about $1\frac{1}{2}$ grs. as on Day 1.

If there had been no dyspepsia on Day 2 there would have been a rise of urea; a more marked rise of acidity and the rise in the excretion of uric acid would not have begun till Day 3 or 4.

If a man eats a dinner for which he feels better, there will be a rise of urea and acidity, and the rise of uric acid will be postponed; but if he gets dyspepsia after the dinner, whether from excess in food or drink, or from other external or accidental cause, then there will be, as in this figure, little or no rise of urea, and the uric acid contained in the meat taken will pass quickly into the blood, and the excretion in the urine will quickly rise.

There can be no doubt about the introduction of fresh uric acid in the food, but whether that will be excreted at once, or only in two or three days' time, depends on the conditions which affect acidity and so the solubility of uric acid in the blood.

The point of this figure is that with the increased introduction of uric acid and other members of the xanthin group in the meat eaten on Day 2 there goes a correspondingly increased excretion of uric acid in the urine.

As in other figures we see here also the inverse relation between uric acid and the excretion of water: on Day 2 it is true that water is high, although uric acid is rising, but if we look at the figures on each side of the curves we see that the water was 75 cc. per hour in the day hours, when uric acid was probably not very high, and only 66 cc. per hour in the night, when the dinner having been taken, and dyspepsia becoming established, acidity began to fall and uric acid to rise. With the high uric acid of Day 3 there is a marked fall in the water, which is low also on the following day, especially in the morning hours, when the plus excretion of uric acid doubtless continued. On Day 5 there is a rise of uric acid, and also a rise of water, but here again the figures show that the water was scanty in the day hours, when uric acid was highest, and profuse in the night hours, when it had begun to fall. On Day 6 there is a decided fall of uric acid, due partly to the rise of acidity and partly to want of supplies, and with this there is a further rise of water, which is now profuse in the day hours and not scanty as on previous days, and if the urate excretion could be followed from hour to hour the inverse relation between it and the urinary water would come out still more clearly, and indeed the fluctuations in the excretion of uric acid can be estimated with an accuracy which is often sufficient

for clinical purposes by measuring the hourly excretion of water, bearing in mind that this rule postulates the condition that other things are and remain equal; for obviously, if the supply of fluids in the body is scanty, the relaxation of arterioles, which absence of urates from the blood stream allows, will not cause a diuresis, and conversely when there is an excess of fluids in the blood and

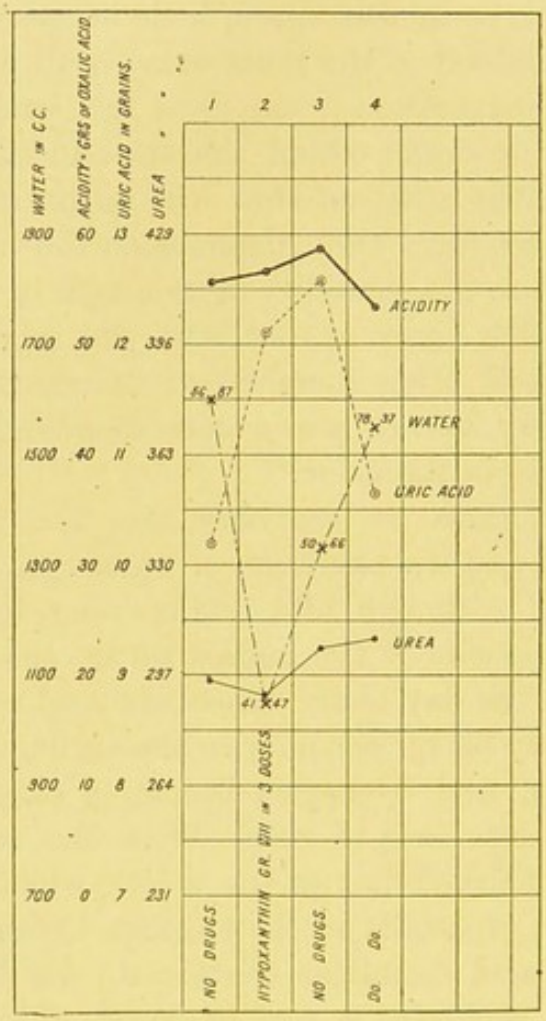

FIG. 17.—EFFECT ON THE EXCRETION OF URIC ACID OF SWALLOWING HYPOXANTHIN.

tissues, which carried to excess becomes pathological (dropsy) a comparatively small relaxation of arterioles will cause a big diuresis.

Fig. 17 shows the effect of 8 grs. of hypoxanthin taken on Day 2, and it appears to increase very markedly the excretion of uric acid which rises on Days 2 and 3 in spite of a slight rise of acidity, and falls again on Day 4 in spite of a fall of acidity.

Note also the inverse relation of the urinary water which falls on Days 2 and 3 with high uric acid, and rises again on Day 4 as uric acid comes down.

If this is so it appears probable that the metabolism of the human body makes short work of the slight chemical differences

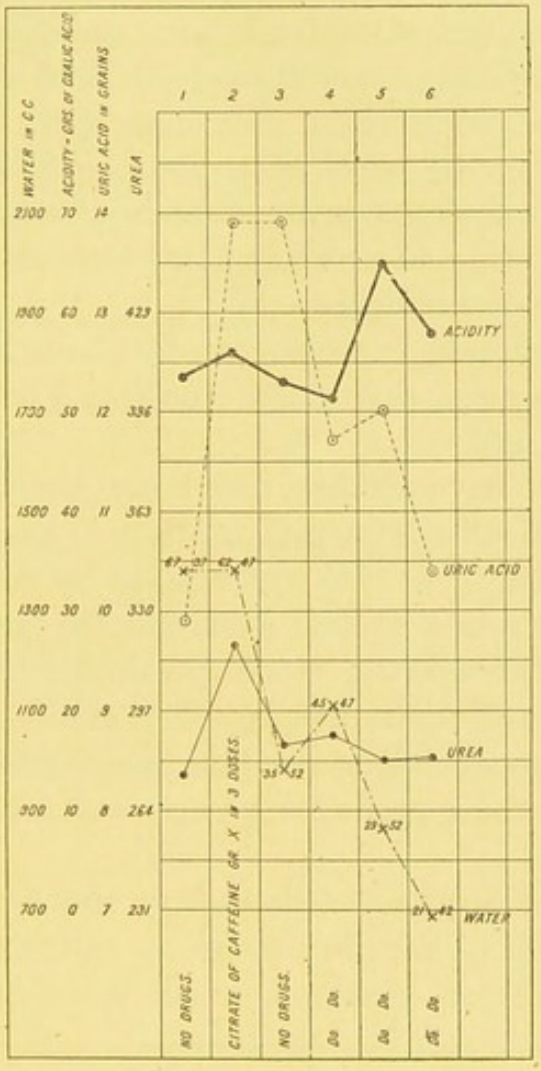

FIG. 18.—EFFECT ON THE EXCRETION OF URIC ACID OF SWALLOWING CITRATE OF CAFFEINE.

between members of the xanthin group, and passes the greater part of them through the blood and into the urine as uric acid. And one very important consideration forces itself in here, though I shall have to return to it again later on, namely, that if members of the xanthin group are thus converted into and must practically be reckoned as uric acid, the estimation of the uric

acid present in any food substance gives only an imperfect record of the amount of uric acid it may introduce into the body; for the xanthin and hypoxanthin remain unestimated. The table, therefore, which I give of the amount of uric acid found in various food substances must be taken only as showing a part of the uric acid which these substances may introduce into the body, and important substances should be put to the more valuable physiological test of taking known quantities by mouth, and estimating the increased excretion of uric acid produced as in the figures I am now describing. (See chap. xvii.)

Fig. 18 shows the effect of a dose of 10 grs. of citrate of caffeine taken on Day 2, namely, a marked and immediate rise in the excretion of uric acid which remains high above urea on all the subsequent days of the figure.

On Day 1 uric acid exceeds urea by about $1\frac{1}{2}$ grs.; on Day 2 it exceeds it by more than 4 grs.; on Day 3 by more than 5; on Day 4 by 3 grs., and so on.

Here then we have another member of the xanthin group (for caffeine is, chemically, trimethyl xanthin—Lea, "Chemical Basis of the Animal Body," p. 175) which taken by the mouth markedly increases the excretion of uric acid, and the amount of that substance passing through the blood. And this result is, I believe, absolutely constant, for as will appear presently I have been able, by administering caffeine, to produce pathological changes in the blood similar to those produced by uric acid when taken in other forms.

An important corollary follows from this figure also, namely, that all vegetable alkaloids similar to caffeine, and which are chemically ureids or xanthins, must be regarded as possible introducers of uric acid into the body.

Fig. 19 show the effect of eating a sheep's thyroid gland, and this also apparently produces on the first, second and third days after its ingestion some plus excretion of uric acid.

The first effect of taking the thyroid was a very marked diuresis: the first dose of the gland was taken at 1.30 p.m., and it did not greatly affect the urine of the day which was 44 cc. per hour, but in the night following it ran up to 138 cc. per hour.

Note that with this big diuresis there was a rise of acidity and urea, and that the uric acid exceeded the urea by almost nothing, that is to say there was no uric acid passing through the blood.

Bear in mind also that acids, mercury, iodides, iron, lead and a host of other drugs which clear uric acid out of the blood, will produce a similar rise of urea and a similar diuresis.

The sequence of causation in the case of this figure was probably somewhat as follows:—Eating the thyroid gland introduced certain nitrogenous substances and certain acids or acid

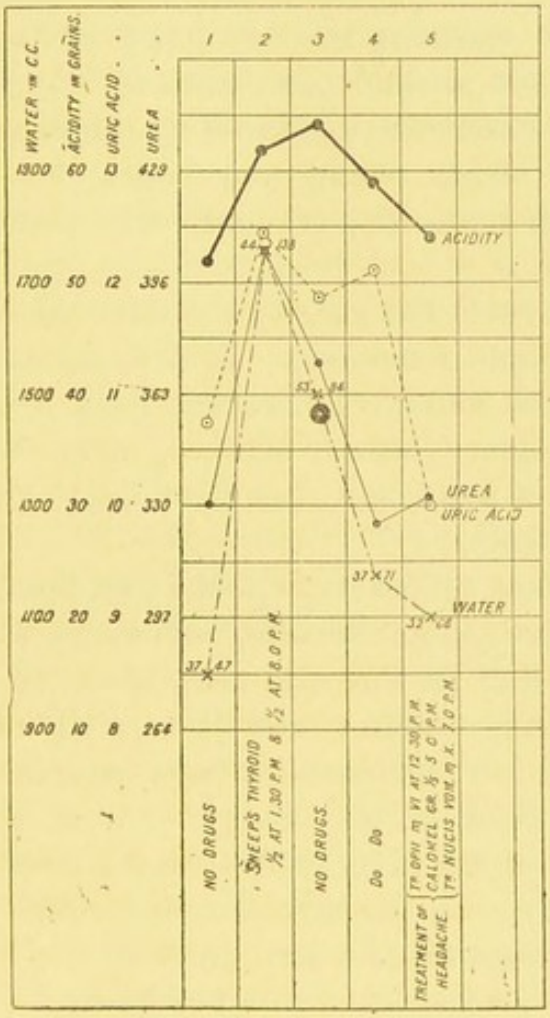

FIG. 19.—EFFECT ON THE EXCRETION OF URIC ACID OF SWALLOWING A SHEEP'S THYROID GLAND.

salts; these produced a rise of urea and of acidity; this latter cleared uric acid out of the blood and allowed the arterioles to relax. With this relaxation of arterioles went a general quickening of metabolism, and a further rise of urea and acidity, and the relaxation of the kidney arterioles allowed of a profuse diuresis because the water had been scanty on Day 1, and fluid had been accumulating in the body.

On Day 3 uric acid exceeded urea by ½ gr., and on Day 4 by more than 4 grs., and it would no doubt also have exceeded it on Day 5, but on the morning of this day there was considerable headache, and drugs which brought down the uric acid had to be taken to cure it.

Note the large excretion of water on Day 2 when uric acid is close to urea, and none passed through the blood, and its steady fall on subsequent days when uric acid rose, and also the extremely scanty water in the day hours of Day 5, when there was a headache and no doubt an excess of uric acid in the blood, though the minus excretion produced by the drugs brought down the level for the whole twenty-four hours; but here the water tells us in which hours the uric acid was scanty and in which profuse.

A dose of uric acid has exactly the same effect (see *Journal of Physiology*, previous reference). It first raises the acidity and produces a diuresis and on subsequent days a plus excretion of uric acid with scanty water; similarly with caffeine there is a diuresis in the first few hours after the dose, followed by plus uric acid and scanty water.

I have, therefore, no practical doubt that the diuresis produced by thyroid glands or their extracts, with which I have made many experiments, is due to the uric acid or other members of the xanthin group they contain, and it is well known that these glands are rich in nitrogenous extractives. (See Professor Foster's "Text Book of Physiology," ed. v., p. 762.) And as we shall see presently in patients treated with these glands or their extracts, we soon get strong symptomatic evidence of the passage of an excess of uric acid through the blood, exactly as we do when uric acid is taken in other forms. (See chap. xii.).

These figures, then, practically show that uric acid, when taken by the mouth whether in food or as an addition to food, passes into the blood, and, when the conditions in that fluid are favourable to its solubility, remains there till it is excreted in the urine; that it is not to any appreciable extent converted (as was supposed) into urea; that the rise of urea which these substances produce is secondary to the rise of acidity which they also produce; and that other acids which introduce no nitrogen into the body produce a similar rise in the excretion of urea.

From these facts I think we may draw a few general conclusions.

First, that the amount of uric acid in the blood of man, and probably of animals also, is not a mere matter of chance, but is always subject to certain definite rules, which to my mind can be summed up by saying that the amount of uric acid in the blood is proportional to the solvent power of that fluid, and its contained salts for uric acid and its salts. Increase of solvent power means increase of urate in the blood, so long as there is urate anywhere in the body to be dissolved; and by influencing the solvent power of the blood we can influence within limits the amount of uric acid it contains; we can also influence it indirectly by the amount of uric acid we introduce ready formed in the food.

Second, excess of uric acid in the blood means contemporaneous excess of uric acid over urea in the urine: though as the urine in the bladder may be a mixture of urines excreted under several different conditions of blood, it must not be expected that the amount in the two fluids will correspond too closely.

This rule probably holds in all cases in physiology, but in pathology there is at least one well-marked exception to it, namely, nephritis; for in this condition the akalinity of the kidney is probably diminished by the irritative processes going on in it, so that there may be (and according to v. Jaksch there is) excess of uric acid in the blood, and yet it may be unable to pass the kidney into the urine. Hence we get in nephritis chronic retention of urates and chronic uricacidæmia (of which the signs are well-marked) without excess of urates in the urine; and this consideration probably explains the relief that is obtained in acute nephritis (see Sir W. Roberts' "Urinary and Renal Diseases," p. 435-6), when the urine is rendered alkaline, so that some of the pent-up urate, which no doubt adds to the kidney irritation, can find its way out in a plentiful supply of solvent.

Third, the quantity of urate in the various organs and tissues seems to stand in a certain order of proportion: thus, the liver and spleen have most, the kidney decidedly less, and the muscles least; the quantity in the blood varies considerably, but, except perhaps in pneumonia, it always contains less than the liver or spleen from the same body.

The quantities found after death in the blood again bear fairly definite relations to certain diseases; in pneumonia cases there is almost sure to be a large quantity; but in meningitis and other

cases in which the temperature is high, and rising at death, there will be very little; again, in death from chronic wasting disease there will be a good deal, especially if there are urate deposits in the joints.

In the case in which the kidney contained so-called uric acid infarcts the temperature was high, and rising at death, which was due to marasmus; we should, therefore, expect very little urate in the blood, because it had been driven out of it, and the infarcts in the kidney probably show us one of the places into which it had been driven, there being, in fact, a gout of the kidney, this possibly being secondary to the irritation of previous uric-acidæmia.

It thus seems to me to be practically certain that when uric acid is found in excess in the blood after death, it was in excess in that fluid at the time of death, and was passing from it in excess in the urine; and the excess in both fluids is due to the action of the same causes which determine excess in them during life.

I have shown that I can alter the amount of uric acid in the urine at any time, and that in addition to the above argument I have good clinical reasons for believing that I alter at the same time the amount in the blood.

That when I increase the amount in the blood by giving an alkali, I at once bring about contraction of the arterioles throughout the body, thus raising the pulse tension and slowing the heart, and causing deficient circulation in numerous organs, the effect of which is soon visible in cold surface and extremities, mental depression or headache, and scanty urine containing a relative excess of uric acid.

If I now reverse the process by giving an acid, I at once relax all the arterioles, and the uric acid is driven out of the blood into the liver, spleen, joints, &c., and if much of it is sent into the latter it generally renders its presence clinically evident by a certain amount of shooting and pricking pain, or more severe irritation up to distinct arthritis; the relaxed arterioles reduce the pulse tension and the heart quickens its pace, the surface and extremities become warm, the mind is clear and tranquil, the urine increases in quantity and shows diminished uric acid.

That the alterations in the amount of uric acid in the urine so produced are alterations of excretion merely, and that the

quantity to be found in the blood at any time depends on its solvent power for uric acid, the amount daily introduced in the food, and the amount previously stored in the liver, spleen, joints and other tissues on which the solvent can act. That when the alkalinity of the blood (*i.e.*, its solvent power for uric acid) is reduced it contains little or none; but when its alkalinity is increased it may contain a very large quantity.

That, as I have previously pointed out, all fluctuations in excretion taken over a long period of time practically balance each other, giving a result near what I believe to represent the real formation of uric acid, viz., 1 of uric acid to 35 of urea.

That though the large excretion of uric acid in splenic leucocythæmia, for instance, looks for a time like excessive formation, it is probably merely the passage out of the body of large amounts of uric acid which were retained in the early stages of the disease. Thus, in a case of this kind I was able to examine after death, I found in the blood .06 per cent., a very large liver and spleen contained between them 100 grains of it, there were urate calculi in one kidney and erosion in the great toe joint, but no deposit of urates there (see "St. Bartholomew's Hospital *Post-mortem* Book," case of N. T., age 32, April 25, 1892). Here the urates were being dissolved and passed out, and some of them unfortunately got deposited in the kidney on the way, and probably the liver and spleen contained much more uric acid earlier in the disease, for in these cases we know that there are often intercurrent pyrexial attacks during which the spleen enlarges (see *Lancet*, vol. i., 1892, p. 965), and during which I would add, the store of urates in the liver, spleen, and joints, and the body generally is increased. So that while I do not deny that a process of which I have no knowledge, viz., excessive formation of uric acid, may nevertheless occur, I am in a position to assert that I believe all my results, as well as those of Professor v. Jaksch, can be explained by fluctuations in excretion, and further, that all the results which can be produced by drugs are in favour of this explanation, but are quite inexplicable on any theory of excessive formation or deficient oxidation.

If, for instance, the plus excretion of uric acid under alkalies or salicylates (figs. 2 and 4) is due to a plus formation, why does it, except under pathological conditions, not continue for more than two or three days? And even in pathological conditions it does not continue long, for in the case of splenic leucocythæmia,

of which I give notes in chapter xii., a course of salicylate of soda sensibly diminished the excretion; while at the first administration of the drug I got excretions of 1 of uric acid for 12 of urea, it gradually diminished as the drug was continued down to 1 to 24 or less; in other words the stores of urate in the body were slowly being reduced.

The facts above pointed out, that the liver, spleen, and joints contain large amounts of uric acid, are in accord with Sir A. Garrod's theory, and with my explanation of my results; and in accordance with these, the amounts in all these organs and tissues can be increased or diminished at pleasure.

That this explanation satisfactorily accounts on the one hand for the well-known physiological fluctuations in the excretion of uric acid, and on the other for the previously recorded relations of a whole series of diseases, as, for instance, the alternation of gouty arthritis (*i.e.*, retention of uric acid going on in the joints and its absence from the blood), with such diseases as headache, epilepsy, mental depression, and glycosuria, with excess of uric acid in the blood and urine. The arthritis corresponding with relaxed arterioles and low tension pulse from absence of uric acid from the blood, and the latter diseases with contracted arterioles and high tension pulse from the excess of uric acid in the blood.

That in all these cases the excretion of uric acid in the urine corresponds with the amount in the blood, and that the facts about these diseases have been recorded by others who had no knowledge of their real relation to uric acid.

It seems to me that it is impossible to explain these facts either on the theory of excessive formation or on that of deficient oxidation, while Sir A. Garrod's dictum in the case of lead, "the blood becomes loaded with uric acid, not from its increased formation, but from its imperfect excretion," serves to explain the whole situation.

It is now, I hope, obvious that we can not only explain all the physiological fluctuations in the excretion of urates and most of the pathological alterations as well; but that in accordance with my law of solubilities we can imitate nature and demonstrate the effects of uricacidæmia on the function, nutrition, and structure of the tissues of the human body to any required extent; and where the urates already in the body are insufficient for our purpose, we can increase them by the simple process of taking them in one form or another, by mouth (see also chapter xii.).

CHAPTER IV.

Uric Acid and Metabolism.

At this point I propose in order to give my readers a grasp of the subject which may be of some practical utility, to state in a few words what we have already learned, and in equally few words what we seem likely to learn in the chapters that follow; leaving them to judge when they have read these chapters whether my statements are sufficiently supported. And I would before doing so remind them again that I am presenting to them no finished picture but a preliminary communication on a progressive research, on a subject which is still plastic in all directions, and with regard to which much still remains to be learned.

We see then as the result of the researches mentioned in previous chapters that the uric acid daily excreted in the urine comes, or may come, from three sources (1) the uric acid or urate formed out of nitrogenous substances along with a certain amount of urea, probably in the proportion of 1 of uric acid to 35 of urea. (2) Uric acid, urates, or other members of the xanthin group, as caffeine and other vegetable alkaloids introduced with the food. (3) Uric acid or urates previously stored in the body which pass into the blood whenever the alkalinity of that fluid favours their solution in it.

I may here state that uric acid in the title of this book and generally throughout the book itself, unless otherwise specified, is used as an inclusive term comprehending uric acid and its salts.

When in the 24 hours urine uric acid is present in the relation to urea of 1 to 35, we conclude that this uric acid was formed along with the urea of that day and passed directly down the ureter into the urine, and that there was no uric acid

furnished direct from the food or from the stores in the body. If any uric acid was introduced in the food, this was not allowed to remain in the blood because the conditions of that fluid were unfavourable to its solubility, and for the same reason no uric acid was taken up from the stores in the body.

If, however, uric acid was excreted in the relation of 1—20 or 25 of urea, we conclude that the excess over formation (1—35) is made up from uric acid introduced with the food or taken up from the deposits in the body.

Under these conditions it is quite easy to understand why all substances which form soluble compounds with uric acid, or increase its solubility in the blood, should increase its excretion; and why all substances which form insoluble compounds with it, or diminish its solubility in the blood, should diminish its excretion.

If on, the other hand, the excretion of uric acid is very low, having the relation to urea of 1—45 or 1—50, we must conclude that some of the uric acid formed on this day met with conditions in the kidney which were unfavourable to its solubility, and was retained there instead of passing at once down the ureter, and we know that the kidneys may contain an amount which varies from a small percentage up to a quantity which is plainly visible to the eye. (See p. 49.)

I thus regard the formation of uric acid in the body as practically constant; while excretion varies partly with the conditions affecting its solubility in the blood and partly with the quantities introduced in the food, or previously retained in the body, *i.e.*, the quantities available for solution.

It is obviously then in our power to control the excretion of uric acid by controlling the conditions affecting its solubility, and also the quantities directly introduced in the food.

From the clinical history of the uric acid headache we learn that at the time of the attack, when there is an excess of uric acid in the blood and in the urine, the pulse is generally slow, and of high tension.

It appears that this is due to contraction of the arterioles and capillaries, of which there is abundant evidence in the cold skin and extremities that accompany the headache. And a very little experimentation will, I believe, suffice to convince anyone that contraction of the arterioles varies directly with the uric acid

that is circulating in the blood. And this contraction of arterioles will produce two results: (1) a rise of blood pressure in the heart and great vessels on the proximal side of the obstructed vessels—high arterial tension, and (2) a deficient circulation and interchange between the blood and the tissues in, and on the distal side of, the obstructed vessels.

It follows from this that all drugs and disease processes which diminish the excretion of uric acid and clear it out of the blood, will lower arterial tension and improve the circulation through all the organs and tissues of the body.

Drugs have already been mentioned, and the most important disease process which has this effect is fever, which diminishes the alkalinity of the blood, and thus prevents its holding much urate in solution.

Conversely, drugs and disease processes which increase the excretion of uric acid and bring it through the blood in increased quantity will raise arterial tension, and diminish or hinder the circulation through all the organs and tissues of the body.

The most important disease processes which produce this effect are Bright's disease, post-febrile conditions, dyspepsia, splenic leucocythæmia, marasmus and the cachexia of new growths, &c., for in all these conditions of low or failing nutrition there is commonly some increase of the alkalinity of the blood rendering it a more than usually good solvent of uric acid; and in post-febrile conditions not only does the blood thus become a good solvent of uric acid, but a large supply of uric acid is present ready to be dissolved, namely, that which was held back and retained during the low alkalinity of the acute febrile period.

Now, other things being equal, a dilatation of the arterioles of the kidneys means a free flow of urinary water, and their contraction means scanty water: for this reason the urine is scanty (30 cc. per hour) during the uric acid headache (migraine) and profuse (60—160 cc. per hour), during the minus excretion of urates which precedes and follows it.

And not only is this true in pathology, but so constant is the relation of contracted arterioles to uric acid, that in physiology also, in every one from hour to hour and day to day the urinary water varies inversely as the uric acid excreted along with it; or to state it as accurately as possible, other things being equal, the more the excretion of uric acid exceeds the relation to urea

of 1 to 35 the more scanty will be the corresponding hourly or daily excretion of water, and *vice versa*, because as we have seen from previous arguments the uric acid which is excreted in excess of formation (1—35) probably passes through the blood on its way to the kidneys.

It follows from this that all drugs and disease processes which diminish the excretion of uric acid and clear it out of the blood must increase the flow of urinary water, and this I believe represents in its simplest terms the *modus operandi* of the great majority of so called diuretic drugs.

And drugs and disease processes which produce or are accompanied by an increased excretion of uric acid will also be accompanied by a scanty excretion of urinary water; so that the hourly excretion of urinary water being known, the greater or less excretion of uric acid can be calculated from it with sufficient accuracy for many clinical purposes.

This relation between uric acid and water can be seen in nearly every figure in this book, and during the years I have been estimating my own excreta I have not met with anything that could really be called an exception to the rule, if one bears in mind that the excretion of water is dependent partly on the relaxation or contraction of arterioles and partly on the supply of water available for excretion, for obviously no amount of relaxation of arterioles will bring about a diuresis when all fluids have been drained from the blood and tissues by vomiting, diarrhœa or perspiration; but conversely slight relaxation of arterioles may produce a marked diuresis when there is an excess of water in the blood and tissues (dropsy).

One to 33 is the old relation of uric acid to urea in excretion, which I arrived at after a few months' work, and it forms the basis of all the curves of excretion in the book. Further investigation now seems to show that while the relative formation of uric acid to urea is about 1—35, excretion varies greatly from this with the amount of urate available for solution previously stored in the body, and with the amount daily introduced in the food.

As the relation 1 to 33 is so close to the probable formation relation 1—35, I have not thought it worth while to alter all my curves by substituting this latter relation, though I may do so in my subsequent work.

With the exception of gout and rheumatism, all the diseases connected with uric acid are due to its effects on arterial tension and the interstitial circulation of organs and tissues throughout the body.

Thus headache, fits, mental depression, and bad temper, as also vertigo and a host of minor functional disturbances, represent the effects of high arterial tension on the intra-cranial circulation.

In saying this, as in all I shall have to say, I wish it to be understood that while I consider uric acid to be a cause, often the most important cause of these disturbances, I should never go so far as to put it down as the only cause; and in the chapters which treat of the cerebral circulation, it will, I hope, be quite evident that other causes may produce similar alterations in the cerebral circulation, and, therefore, similar symptoms.

The well-known symptoms of high arterial tension represent the effects of uric acid in contracting the arterioles and raising the pressure in the arterial system behind them.

Asthma and chronic bronchitis again probably represent some of the effects of high arterial tension and contracted arterioles on the bronchial and pulmonary circulation, and this probably explains the relation so often seen between these diseases on the one hand, and gout and chronic Bright's disease on the other.

Dyspepsia may undoubtedly be produced by contracted arterioles in the stomach and intestines, which inhibit gastro-intestinal digestion and allow putrefactive processes to take their place; and this again will explain at least part of the relationship between dyspepsia and such troubles as headache, epilepsy, and mental depression, or between dyspepsia and Raynaud's disease, or paroxysmal hæmoglobinuria.

In the liver again, just as in the stomach or intestines, we may obviously get more or less stasis or congestion as a direct or indirect result of the circulatory changes produced by uric acid.

Precisely the same thing applies word for word to the kidney, and here we have a very obvious and tangible result of the changes so produced in its circulation, in the fluctuations in the urinary water previously referred to.

The same thing is seen in the salivary and probably in all other glands; and, in accordance with this, when a uric acid headache is present and the urinary water is scanty, the mouth

also tends to be dry or sticky, and the saliva is scanty; and when the headache has been cured by acids, opium, mercury, iodides—any of the drugs which clear uric acid out of the blood—not only is there a diuresis, but the saliva also becomes relatively profuse.

In the muscles, also, there can be little doubt that uricacidæmia produces deficient circulation and deficient removal of waste products, though probably the disinclination for muscular exertion, which is so marked a feature in attacks of migraine or mental depression, is due rather to the condition of the nerve centres than of the muscles; still, I think that cramps and other slight disturbances of muscle function are not improbably sometimes due to the deficient circulation of uricacidæmia.

The skin also has its circulation and nutrition very markedly influenced by uric acid, as witness the very pale and cold surface commonly seen in attacks of migraine, and in conditions in which there is for some time a continual excess of uric acid in the blood, as in post-febrile conditions, marasmus, and chronic dyspepsia, the nutrition of the skin may be interfered with to an extent which may account for not a few eruptions, especially ulcerative eruptions, slow healing of wounds and other troubles; and in these conditions I am in the habit of ordering drugs that clear the blood of uric acid, in full confidence that if there is no organic disease I shall be able to improve the nutrition of the skin and facilitate the healing of wounds and the clearing up of rashes. Such a consideration explains the frequent time connection between skin eruptions and menstruation in women, for menstruation is nearly always accompanied by a certain amount of dyspepsia and lowered nutrition, and the uricacidæmia which results from it. (See chap. xii.).

That uricacidæmia affects the nutrition of the extremities as well as the skin is seen in the pale, cold hands and feet which are so marked a symptom in migraine, in the "dead hand" of Bright's disease, and the still more marked alterations in nutrition met with in Raynaud's disease.

Last, but not least, an excess of uric acid seems to produce changes in the nutrition and structure of the blood itself, so that just as it is possible to cure anæmia by giving iron, it is also possible to produce anæmia by giving uric acid, and where the two are given together the uric acid overpowers the iron, and the

blood either remains *in statu quo*, or deteriorates, and in my own person not only does my blood fraction— $\frac{\text{hæmoglobin per cent.}}{\text{red cells per cent.}}$ vary in value from day to day with the quantity of uric acid passing through my blood, but it is possible to make it vary up or down at pleasure by giving uric acid or iron as required.

When the excretion of uric acid exceeds the relation to the urea excreted along with it of 1 to 35 there is some excess of uric acid in the blood (uricacidæmia), and this excess is proportional to the extent by which uric acid exceeds this relation to urea, and proportional also to the absolute quantity of urea. Thus an excretion of 1—25 on a total urea excretion of 350 grs. a day will furnish 4.0 grs. of uric acid to pass through the blood on that day, while an excretion 1—25 in relation to an excretion of 600 grs. of urea will furnish 6.9 grs. of uric acid to pass through the blood. And it appears that the contraction of arterioles, and all the symptoms and phenomena which are secondary to this, are proportional to the absolute quantity of uric acid which is present in the blood from hour to hour—in other words, a man with low urea may excrete 1—25, or even 1—20, of uric acid without having enough passing through his blood to produce any ill effects. And I am myself a good illustration of this point, for though my excretion (see figures previously given) averages considerably over the relation 1 to 35 (that is to say, I excrete all the uric acid I form, and also probably all, or nearly all, I introduce ready formed in food), yet because my urea is low the absolute quantity of uric acid passing through my blood is but rarely sufficient to produce much contraction of arterioles, and the headache and other symptoms which are due to this.

In place of rheumatism and gout I see but one disease, an arthritic irritation due to the presence of urates, which under some circumstances will be limited to one joint (gout), or affect several joints contemporaneously or in succession and the heart also (rheumatism).

Ebstein and other experimenters have shown that the introduction of urates in solution into the tissues produces local irritation, and it rather appears that the irritation is greater when the urates are in solution, than when they are deposited in solid form. Indeed, we know that it is no very uncommon thing to find in the *post-mortem* room a toe joint plastered with urates when the patient had complained of no local irritation, and even

given perhaps no history of gout. The urates had evidently been there some time, and had been causing no trouble. On the other hand the ingestion of a little acid wine or beer will cause, say often within half-an-hour, the retention of some urate (probably in solution) in certain joints, which from hard work or previous irritation are less alkaline than their fellows, and thus quickly bring about considerable pain and inflammation, which, whether it is called gout or rheumatism, is due to urate irritation. I have scores of times produced some such joint irritation in myself, knowing full well every step in the chain of causation; and having this knowledge, I have very many times been able to recognise the causation of joint irritation in gouty or rheumatic patients, by drugs given them by others, or by myself, for other purposes.

Further, I will undertake to produce an arthritis, which shall be clinically indistinguishable from gout or rheumatism, in any member of the profession who is in good general health and will follow my instructions. All that it is necessary to do is to get a little uric acid into the blood, and when one can see by the slow pulse, scanty urine, and more or less headache and mental depression, that it is actually present there, one must administer as quickly as possible some acid or other drug which interferes with the solubility of uric acid, and drives it out of the blood into the tissues. It will probably also be necessary to work or produce some slight irritation in, or in the neighbourhood of the joints we wish to be most affected; thus a man who gets gout because he drinks some extra pints of beer on Saturday night, gets it in the wrist of that hand which he has used most in his trade that evening; and we must imitate nature to this extent if we wish to produce the clinical picture of gout. But it is just the same with all the other diseases I have mentioned; each one of them can be produced or intensified by the intentional introduction of uric acid into the blood, bearing in mind the laws which govern its solubility in that fluid. So that if anyone is in doubt whether his headache is due to uric acid, he has only to swallow certain quantities of the substance under conditions which do not interfere with its remaining in solution in the blood, and convince himself one way or the other. And the same method may be used for the investigation of many other diseases, and, as will be seen presently, I have myself applied it to investigate the causation of anæmia (chapter xii.).

In attempting to estimate the effects of uric acid on the metabolism of the body as a whole, it must never be forgotten that the depressant effect it produces tends to increase itself, so that once the ball is set rolling it will go on down the hill. Thus uric acid is commonly in excess in the blood, because that fluid is more than usually alkaline (*i.e.*, a more than usually good solvent of uric acid); but the effect of an excess of uric acid in the blood is a diminution of the capillary circulation in all the organs and tissues of the body, and as results of this we get, among other things, diminished digestion and absorption of food, and a diminished interchange between the blood and the tissues, that is, a general slackening of metabolism, and this in turn brings about a lessened formation of urea, and of acids and acid salts which usually keep pace with urea. But falling acidity means increased alkalinity of the blood and, so long as plenty of urate is available for solution, more and more marked uric-acidæmia; and thus depression of mind, body and metabolism gets worse and worse, and there seems to be no end to it. But if, before the process has gone very far, and before depression of metabolism has led, as it ultimately does, to much atrophy of tissue, a drug is given, which clears the blood of uric acid, the process may be quickly and completely reversed, for the moment the blood is cleared of uric acid, there is again a free circulation through all the organs and tissues; digestion and absorption of food are resumed, and free tissue metabolism goes on; up goes the formation of urea and of acids, a steady and progressive upward metabolism is started, and the blood is kept clear of uric acid.

I have often been asked by other observers whether the effects of small doses of drugs which clear the blood of uric acid are not out of all proportion to the quantity taken, why does a very minute dose of a nitrite, a few grains of a sulphate, or a small raction of a grain of calomel, relax the arterioles all over the body, cure headache or mental depression, and alter the whole condition of the sufferers? Truly the effect is out of all proportion to the dose.

But if we remember the facts just stated, that each of these drugs, if it is able to clear the blood of uric acid for only a minute or two, starts an upward metabolism which progresses long after the direct effect of the drug has come to an end, we shall have

no difficulty in understanding the way in which these minute doses act.

The drug is like the percussion cap in the cartridge: it does not furnish the force which drives the bullet; it supplies however the spark which ignites the powder. Exactly the same explanation applies to the fact that an apparently insignificant dose of a drug will sometimes produce severe and long-lasting pains in the joints; here again the drug merely started a process which continues long after it has ceased to act.

It has been suggested by several of those who have done me the honour to review some of my writings on these subjects, that I have, to some extent, been led away by my personal interest and experiences to attach an undue importance to the rôle of uric acid in the production of disease.

And the suggestion has found a ready echo in my own mind, for it has often appeared to me very probable that I might fall into this error.

In taking stock of my position, as I have done in this volume, and more especially in this chapter, I feel that while I am by no means free from the ordinary errors and sources of error that affect humanity, I can honestly say that I have spared no pains in the past and will spare none in the future to test in the most rigid manner possible all the assertions I have made; and that I made none at all until the evidence appeared to me to be very strong indeed.

For these reasons I have been truly delighted to find that uric acid taken by mouth is at once absorbed and added on to the urates in the blood and tissues of the body; as this seems to place within our power the means of applying the experimental method to the causation of disease by uric acid.

I thus obtain not only a very convenient power of making more accurate experiments on myself; but anyone who doubts what I say with regard to the power of uric acid in producing changes in circulation, nutrition and metabolism, can very easily test most of the points in his own person.

I believe that it is now quite possible for any one who wishes to do so to raise his arterial tension, slow his pulse, and make his urine per hour scanty simply by swallowing uric acid. But he must bear in mind that the first effect of uric acid taken by mouth is to raise the acidity of the urine and diminish the alkalinity

of the blood, so that it drives uric acid out of the blood, and diminishes the excretion of that substance in the urine, and while it does this it lowers arterial tension, quickens the pulse and increases the excretion of urine; so that a dose of uric acid, hypoxanthin, or caffeine, will cure a uric acid headache. Next day, however, or as the acidity falls again, uric acid passes in excess into the blood, and the picture is reversed.

And I regard such an experiment made by man on his own body, as an infinitely better guide to the effects of uric acid on the arterioles than an injection of any quantity of uric acid into the vessels of animals.

For even if I could inject, say, 10 grains of uric acid into my own blood stream, we should get a relaxation of arterioles and a fall of tension rather than a rise; and further, unless my blood had been previously rendered strongly alkaline, this uric acid would not remain in it more than a very few moments at most; but would quickly be retained in the liver, spleen, joints, and other tissues, causing some gouty pains probably, but no rise of arterial tension.

To affect arterial tension with uric acid, you must first of all introduce it into the body, and then bring it through the blood in combination with alkali.

On the other hand, as I have shown, the introduction of alkali into the blood will produce no effect on arterial tension if there is no uric acid to combine with it; while mere absence of uric acid from the blood, owing to its previous removal by excretants, will allow of relaxed arterioles, lowered tension, quick pulse, profuse urine, and improvement in value of the blood decimal. (See also Fatigue, chap. viii.)

We may sum up this chapter then by saying that uric acid acts as a factor in the causation of disease in one of two ways—

(1) As a direct local irritant when it is present in any tissues in considerable quantity and probably still in solution.

(2) As a contractor of arterioles and capillaries affecting on the one hand the circulation and nutrition of all the organs and tissues of the body, and on the other, producing high arterial tension which directly affects the heart and the vessel walls, and otherwise influences the intra-cranial and thoracic circulations.

CHAPTER V.

Pulse Tension.

As previously remarked, Dr. Liveing has recorded ("Megrim or Sick Headache," p. 329) that several observers have noted the pulse during an attack of megrim to be slow and of high tension (see fig. 26). And very soon after I found out the relation of this headache to uric acid, and the fact that by influencing the uric acid I could produce or remove the headache, I also noticed that when I altered the uric acid, I altered at the same time the rate and tension of the pulse, so that I eventually formulated the conclusion (*British Medical Journal*, January, 1889, p. 291) "that, *cæteris paribus*, arterial tension varies with the amount of uric acid that is circulating in the blood," with the rider that, in so far as it depended on uric acid, it was in my power to alter it, in either direction.

I thus came to believe that uric acid not only accounted for the headache, but also for the high tension pulse and cold extremities that so often accompanied it, and that as uric acid contracted the arterioles and capillaries, and so raised the tension, it produced slowing of the pulse, in accordance with Marey's law that pulse rate varies inversely as arterial tension. Thus he says, "Le cœur bat d'autant plus frequement qu'il eprouve moins de peine a se vider," and then he goes on to explain that the chief obstacle to the heart's systole is the resistance "que le sang eprouve a s'ecouler des arteres dans les veines a travers les petits vaisseaux;" and again he says, "La vitesse du sang augmente si la force du cœur augmente, ou si la resistance des petits vaisseaux diminue," and then he expresses the effect of the arterial tension, produced by the resistance in these little vessels, on the rate of the heart's action, by

saying, "le cœur précipite ses battements à mesure que la tension arterielle leur fait moins d'obstacle." ("Circulation du Sang," pp. 315—336.)

Then as to the signs of "forte tension artierielle," he mentions "pulsations rares, le cœur se vide difficilement, le penetration du sang dans les arteres est lente—le dicrotisme n'a que peu d'amplitude;" and again "Le resserrement des petits vaisseaux cause primitive de cette tension elevee des arteres se traduit par le diminution du volume des extremities par la moindre coloration des teguments, par l'abaissement de la temperature peripherique"[1] —in a word, all the signs of the uric acid headache and the conditions to which it is related.

If my premises are good, and my deductions sound, and if uric acid really influences the circulation to the extent which I have been led to believe that it does, it follows that uric acid really dominates the function, nutrition, and structure of the human body to an extent which has never yet been dreamed of in our philosophy, and in place of affecting the structure of a few comparatively insignificant fibrous tissues in which it is found after death, it may really direct the development, life history, and final decay and dissolution of every tissue, from the most important nerve centres and the most active glands, to the matrix of the nails and the structure of the skin and hair.

If we turn to physiology, we find that the excretion of uric acid varies inversely as the acidity of the urine, and I now show a curve which gives approximately the acidity of the urine, in periods of three hours, for a single day (fig. 20).

This shows that the acidity of the urine is high in the early morning hours, gradually falling toward 6 a.m. It is low after that, reaching a minimum about 9 or 10 a.m., and then rising slowly till 2.30 or 3 p.m., when it again falls to a second minimum, about 6 p.m., after which it rises to its night maximum.

The morning fall is already well known, and the normal urine may be very slightly acid, or even alkaline at this time — the "alkaline tide" of Sir W. Roberts. I have found that there is an almost equally constant fall of acidity from 3 to 6 p.m., which I have ventured to call the second or afternoon alkaline tide, and

[1] Prev. ref., p. 549.

in the same way I have spoken of the high rise of acidity at night as the acid tide.

Now the excretion of uric acid, as I have said, varies inversely as the acidity, and its greatest hourly excretion occurs in the alkaline tide of the morning, and the smallest hourly excretion in the acid tide of the night—facts which are very well known to physiologists. For instance, Sir W. Roberts says ("Urinary and Renal Diseases," p. 71): "It is seen [in a table which he

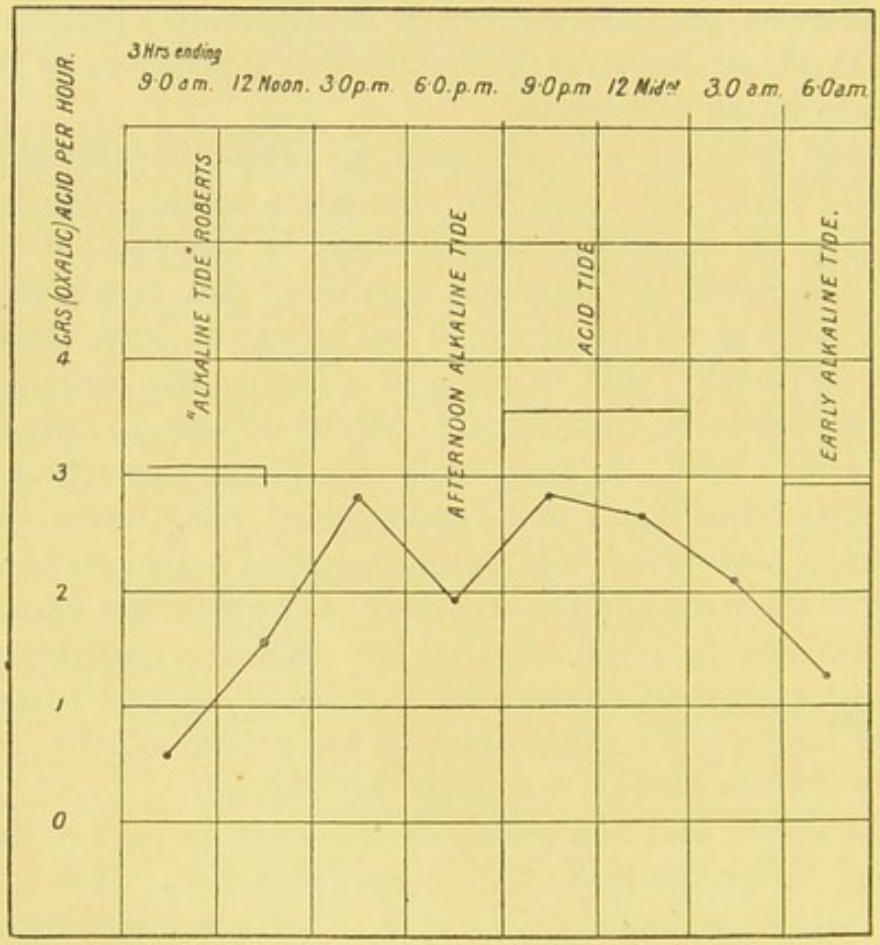

FIG. 20.—DIAGRAM OF ACID EXCRETED IN THE URINE IN TWENTY-FOUR HOURS: THE TOTAL ACID IN THREE HOURS BEING DIVIDED BY THREE.

gives] that the absolute quantity hourly secreted is three times greater during the period of the alkaline tide than during the other periods," and my results are identical with his. So that not only is it possible, as I have shown, to alter the excretion of uric acid from hour to hour by the exhibition of acids and alkalies, but the whole excretion of uric acid in physiology and throughout life is dependent on the same fact.

I have no doubt, from my knowledge of the action of drugs on uric acid, that its excretion is simply a matter of solubility. It is very soluble in alkalies, but very insoluble in acids; all substances which increase its solubility increase its excretion, and *vice versâ;* hence it comes about that though uric acid and urea are probably being formed all day and all night in exactly the same relative proportions—1—33 or 1—35—the excretion of uric acid is far greater in the alkaline tide of the day and far less relatively to urea in the acid tide of the night.

Formation never varies, but excretion varies inversely as acidity, hence it comes about that the uric acid formed between 6 p.m. and 6 a.m. is to a large extent held back in the body and retained; but in the "alkaline tide" of the morning not only is all the uric acid formed at once excreted, but it is reinforced by the whole of the uric acid retained in the night, producing the greatest hourly excretion of the whole twenty-four hours (a well-known fact). If the plus excretion of the two alkaline tides balances the minus excretion of the acid tide, all the uric acid formed in the twenty-four hours is excreted in the same period, and all goes well. But when the general run of acidity is high (as when much nitrogenous food is taken, with a liberal allowance of acid beers and wines) then there comes a time when the morning fall of acidity is not sufficiently marked and prolonged to allow all the uric acid retained in the night to find its way out, and then the excretion of the twenty-four hours falls short of formation and introduction, and uric acid accumulates in the body; and if a fraction more than 1 gr. is thus held back every day, an ounce would be accumulated in a year. Conversely, when the general run of acidity is low (as when little nitrogenous food is taken and no extra acids are indulged in), not only is all the uric acid formed in twenty-four hours excreted in the same period, but the excess of solvent alkali takes up uric acid that has been previously retained, gets it into solution in the blood, and passes it out by the kidney; so the excretion of uric acid in the twenty-four hours exceeds the formation in the same period, and uric acid is removed from various tissues and organs (liver, spleen, joints, and fibrous tissues) in which, during a previous period of high acidity it had been retained.

The excretion of uric acid is thus seen to be a simple matter of solubility, and all things which increase its solubility increase

its excretion and *vice versâ*, both in physiology and pathology; and in experiment it is easy to alter its excretion at any time, and in any direction by the application of this rule.

It follows from this and my previous arguments and deductions, that uric acid is present in excess in the blood during certain hours of each day, both in physiology and pathology, for even in physiological conditions the uric acid retained in the acid tide of the night must (see previous arguments, chap. ii., pp. 13-16) pass through the blood on its way to the kidney.

Uric acid is therefore in excess in the blood daily from about 6 a.m. to 12.30 or 1 p.m., and again from 3.30 to about 6.30 p.m.; in those whose formation is small, and their supply of alkali (from vegetable food and fruits) large, the excess will never probably be very great (hence my immunity from uric acid headache on a vegetable and milk diet), but in those whose formation is large and their acidity high, the excess may from time to time, when the acidity is temporarily reduced, be very great (hence they may have severe headaches, epilepsy, mental depression, &c.)

But I said at the beginning of the chapter that arterial tension is directly as the uric acid in the blood, and that the pulse rate varies with arterial tension in accordance with Marey's law.

It follows, therefore, that the pulse in physiological conditions will be slower and of higher tension from 6 a.m. to 12.30 p.m., and again from 3.30 to 6.30 p.m. than in any other portion of the twenty-four hours, and that it will be quicker and of lower tension in the acid tide of the night than at any other time.

My researches have left no doubt in my mind that this is the case, and I am confident that all clinical observers will uphold me in this statement, and Marey himself says: "On observe le matin au reveil un ralentissement du pouls avec tous les caracteres de la forte tension: le soir au contraire le pouls s'accelere et presente la caractere de la tension faible." ("Circulation du Sang," p. 350.)

I have heard it suggested that the pulse is slow after breakfast because a large amount of the products of digestion are passing into the blood, and because of the changes which digestion effects in the circulation, but the pulse is quite as slow in the alkaline tide which precedes breakfast often by one or two hours.

Again, digestion and its direct effects (whatever they may be) on the circulation are equally present after dinner, but the pulse is not so slow or the urine so scanty as after breakfast because (see fig. 20), the acidity is higher. There is less uric acid in the blood, and its effects on the arterioles are proportionately reduced.

But not only is the pulse affected in this way by the uric acid, but it in turn affects the circulation in, and the function of, several important organs in a way, and to an extent which leaves little doubt as to the real existence of the cause and effect of which I have been speaking.

I have previously mentioned that the urine of the uric acid headache which contains excess of uric acid is scanty, and of high specific gravity, and that conversely the urine which is passed after the headache goes or is driven off not only contains little uric acid (a small relative and absolute hourly excretion), but is copious, watery, and of low specific gravity; so that it appears, as I have stated it, that "the urinary water varies inversely as the uric acid excreted along with it."

It appears to me that a simple explanation of this fact may be obtained by supposing that when uric acid contracts the arterioles and raises the tension, it contracts, among others, the arterioles of the kidney, and so shuts off the water.

If this is so, drugs such as digitalis and erythrophlæum, which contract the arterioles and raise the tension, should diminish the urinary water, and I have been much interested, and have quoted in several papers from Dr. Brunton's researches with these drugs, which show that this is the case. Thus he says ("Pharmacology and Therapeutics," ed. iii., p. 430):—"Thus Mr. Power and I found that on injecting digitalis into the circulation of a dog, the blood pressure rose, but the secretion of urine was either greatly diminished or ceased altogether. Here it is evident that the renal vessels had contracted so much as to prevent the circulation through the kidney, notwithstanding the rise that had taken place in the blood pressure. After a while the blood pressure began to fall, and then the secretion of urine rose much above its normal, showing that the general blood pressure was then able again to drive blood into the kidneys."

And Dr. Brunton's figure of the excretion of urine during the action of erythrophlæum, which he has most kindly allowed me to reproduce here, shows exactly the same thing (see fig. 21).

It seems that in the case of digitalis, and other drugs of similar action, the diuresis has been wrongly credited to the rise of pressure, which Dr. Brunton's figure and facts show that it does not completely correspond to. The first effect of these drugs is to hold back and retain in the body some water, and then, as the arterioles are relaxed and the blood pressure falls, this passes out, producing a marked temporary diuresis.

Digitalis and erythrophlæum thus exactly parallel what occurs in the uric acid headache, in epilepsy, hysteria, and other

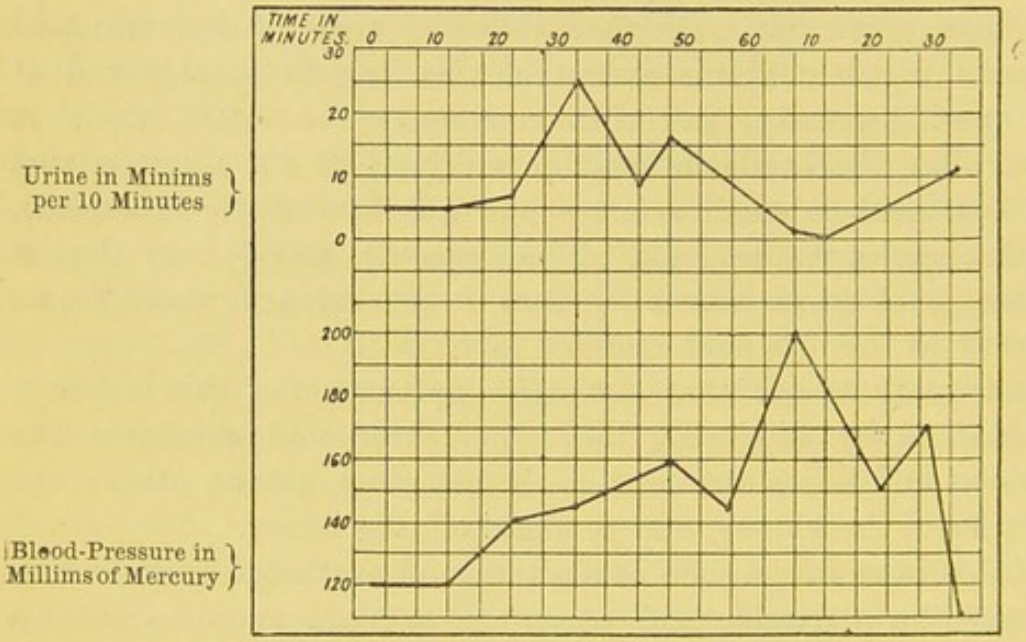

FIG. 21.— CURVES SHOWING THE EFFECT OF ERYTHROPHLÆUM UPON THE BLOOD PRESSURE AND SECRETION OF URINE. From Dr. Lauder Brunton's Paper in *Phil. Trans.*, vol. clxvii.

conditions accompanied by high tension pulse and contracted arterioles, and urinary water is thus inversely as the uric acid excretion, and inversely as the contraction of the arterioles.

In future chapters we shall see that when uric acid contracts the arterioles it affects the function of many other organs besides the kidneys, and produces results which bear exactly the same relation to the excretion of uric acid that the urinary water does.

The pulse is slowest and the urinary water least in the day, especially in the alkaline tide after breakfast, and the pulse is quickest and the urinary water most in the acid tide of the night, and we shall see that this rule, which holds in physiology,

dominates still more strongly in pathology, where the power of uric acid is much greater, because its fluctuations are more marked. Thus the water in the day may be only 40 to 50 cc. per hour, while that of the night is 70 to 80 cc. per hour, this being just the reverse of the excretion of urates which is most in the day and least in the night. Further, by altering the time of the urate excretion one can alter that of the water excretion also. To do this let any one take such a dose of alkali (not lithia, for reasons given in previous pages) as shall render his urine alkaline all through the twenty-four hours, and continue this for seven to eight days. After two or three days he will find that the urine is now much the same in quantity per hour both night and day, that it is not scanty during the day and morning hours, and therefore not profuse at night. And the reason of this is obvious ; the plus excretion of urate which normally takes place in the alkaline tide of the day is the result of the retention of urate during the acid tide of the previous night, but he has been taking alkali for several days, and there is now no acid tide at night, and its effects have disappeared with it. There is now little or no retention of urate at night, hence there is no plus excretion of urate in the alkaline tide next day, the arterioles are therefore not contracted and the urinary water is not scanty, indeed, it may now be quite profuse by day, this being just the reverse of what takes place when the acidity is normal. In this way, by controlling the urate we can control the water, and alter at pleasure the rate of the heart's action and the tension of the pulse.

With regard to the flow of urine I will here give a few figures. Thus, on the 8th of May, 1891, uric acid was high, having a relation to urea for the whole twenty-four hours of 1 to 22. This means that there was a large excretion of uric acid, some 4½ grs. of it being washed out from deposits in the organs and tissues, and passing through the blood on its way to the kidney.

Now, practically, a large excretion of uric acid on any day means a large excretion in the alkaline tide periods of that day.

And now look at the urinary water on this day ; with a very large excretion of uric acid the water of seventeen hours of the day equalled only 600 cc. or 35 cc. per hour, a very low excretion ; and during the seven hours of the night it was 570 cc. or

81 cc. per hour; the water held back during the day was, to a large extent, passed out as soon as the high acidity of the night period cleared the blood of uric acid (the exact parallel of digitalis).

Then take another day, as May 11, when the uric acid bears nearly its normal relation to urea, namely 1 to 32; there would be but a slight excretion in the alkaline tide, and, in accordance with our premises, little or none passing through the blood; and, under these conditions, the water for seventeen hours of the day was 1370 cc., or 80 cc. in the hour; while the excretion in seven hours of the night was 630 cc. or 90 cc. per hour; on May 8, the urine per hour at night rose to two or three times its amount per hour in the day. On the 11th, the night urine was only one-eighth more per hour than that of the day; on the 8th, water was held back in the day and passed out at night; on the 11th, it was passed freely in both periods; hence, as I have said, the urinary water is inversely as the uric acid excreted along with it, and inversely as the amount of it in the blood, because the greater the amount of uric acid in the blood the more contracted are the arterioles of the kidney.

It will thus be seen that my assertion that arterial tension varies directly as the uric acid in the blood has other foundations besides observations of the pulse rate and tension, though, as we shall see presently, these are conclusive enough; and followed from hour to hour the same thing is seen; the urinary water is inversely as the uric acid, and if the uric acid is intentionally increased or diminished, the water alters in the opposite direction.

This brings me to the action of drugs and the experimental aspect of the question, but the same laws hold good.

(1) All substances which increase the solubility of uric acid increase its excretion and *vice versâ*.

(2) Substances which increase its solubility, bring it into the blood in large quantity, contract the arterioles, slow the heart, and diminish the urinary water.

I have already gone into the action of drugs on uric acid; I shall here merely mention their effects as regards the pulse rate and tension, and the secretion of urine.

First of all, drugs which increase the excretion of uric acid; alkalies, as soda and potash, increase the excretion of uric acid

and diminish the urinary water; but as their effect on uric acid is coming to an end (possibly because all the immediately available uric acid is cleared out) there is more or less diuresis, the water which they at first held back passing out. This is illustrated in the figures of May 8th just mentioned. This was a natural excretion (or fluctuation in excretion) apart from drugs, but precisely the same thing would have occurred if I had given alkalies to increase the uric acid.

Salicylates again bring excess of uric acid into the blood, and while the excess of uric acid is being passed in the urine, it is not very copious but tends to be high-coloured and scanty; hence as has been noted by several observers (Huber in *Deutsch Archiv. fur Klin. Med.*, xii., p. 129, and Stiller, *British Medical Journal*, vol. i., 1890, p. 808), as well as myself, the great diuresis with salicylates comes on the second day of their administration, when the excretion of uric acid and the amount of it in the blood is beginning to diminish from want of supplies.

Diuretin=Salicylate of sodium and theobromine (=dimethyl-xanthin) appears to me to produce diuresis in much the same way that salicylate of soda produces it, namely, by clearing the blood of uric acid. I made some experiments with tabloids of this substance, kindly sent me by Messrs. Burroughs, Wellcome, and Co., and my results show that just as with salicylate of soda there is no diuresis on the first day of taking the drug, on the contrary, the uric acid rises and the water falls, but there is a diuresis on the second or third day, when the excretion of uric acid comes down again. I have no doubt, therefore, that the diuresis is due to the salicylate element, or rather to the action of this element on the excretion of urates, and this explains the fact, noted by some observers, that the diuretic effects of diuretin may continue after ceasing to take the drug. (Massalongo and Silvestri, "Reforma Medica," March, 1893.) On the other hand if the diuresis were due to the dimethyl-xanthin it would occur soon after the drug was administered, as is the case with uric acid, hypoxanthine, caffeine, &c. (See previous remarks on these substances.)

With phosphate of soda again the water fluctuates in accordance with the excretion of uric acid, and independently of the amount of the drug; when the drug increases markedly the excretion of uric acid the water tends to be low.

A large excretion under the phosphate or a salicylate is not, as I have remarked before, accompanied by any headache, but the excess of uric acid in the blood keeps the arterioles moderately contracted and pulse tension somewhat high, though to nothing like the same extent as would be the case if the same amount of uric acid was being excreted under alkali; so that I have supposed that the compound formed by uric acid with salicylates and alkaline phosphates has less effect on the arterioles than the combination with simple alkali, but probably even when salicylates or phosphates are in circulation there is always some urate combined with alkali, and this may account for the effect on the arterioles in all cases.

Of drugs which diminish the excretion of uric acid, opium is perhaps the most important; I believe that it acts as an acid, which in nature, apart from drugs, is the most important factor. The pulse of opium well being and of the rebound next day are found in fig. 23.

The effects of morphine in raising the acidity and causing retention of uric acid are shown in fig. 10, and along with these go the quick low tension pulse, B in fig. 23, which again is the sign of a free capillary circulation throughout the body; its effects and further signs being mental well being, bodily strength and power of endurance, and a free excretion of urinary water. Here, again, all these effects are due to the action of the drug on uric acid, and correspond with it. Thus, one morning before breakfast when my pulse was slow and of high tension (rate 58), I measured the urine in the hour ending 8.15 a.m., and found it 53 cc., I then took ♏ vi. of tincture of opium, in tabloids, the pulse at 8.15 being 62, and I collected the urine of the next hour ending 9.15, no food or drink having meanwhile been taken since the previous evening. At 9.15 a.m. the pulse was 72, markedly softer, and with a larger dicrotic wave than the pulse trace at 8.15, and the urine passed in the hour was 234 cc. Obviously then the comparatively scanty urine at 8.15 a.m. was not due to want of water in the body, but to contraction of the arterioles with which it corresponded.

Mercury I have also written about, and as to the facts that it reduces arterial tension, and produces diuresis, the writings of Broadbent and Jendrassick sufficiently testify. I believe, as I have said, that these effects are simply and solely due to its

action on uric acid, furnishing in this respect but a single instance of my general laws above stated. Fig. 22 shows the pulse trace, A before and B during the action of mercury, the latter corresponding with a minus excretion of uric acid and diuresis. (See fig. 11, p. 36.)

Lithia is one of the most interesting of the other drugs which produce the same results. I have given above, chapter ii., p. 29 and 30, my explanation of the fact that it reduces the excretion of uric acid.

Lithia markedly diminishes the acidity of the urine, and yet, unlike the other alkalies which produce this result, it reduces arterial tension, quickens the pulse, and produces diuresis. Here again we see that the effects on the pulse tension and flow of

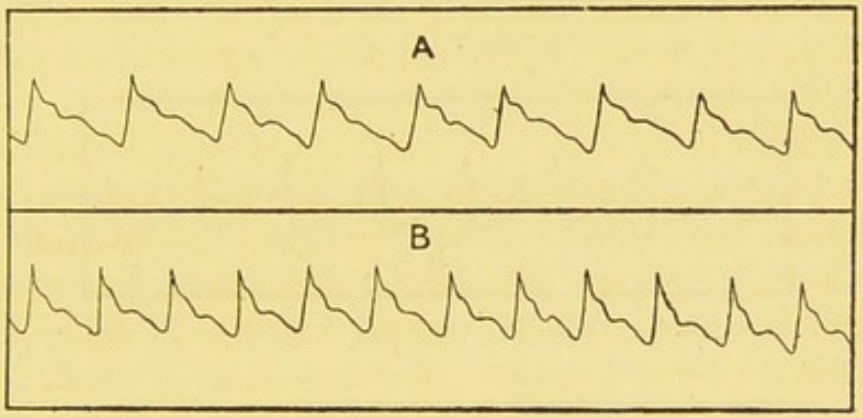

FIG. 22.—PULSE TRACES SHOWING THE TENSION A BEFORE AND B DURING THE ACTION OF MERCURY.

urine depend on the uric acid, and not on the acidity, alkalinity or other power of the drug. Soda and potash raise the tension of the pulse and diminish the urine, while it becomes more alkaline. Lithia diminishes pulse tension and increases the urine, while it becomes also more alkaline, but soda and potash increase the excretion of uric acid. Lithia diminishes it.

Again, as before remarked, if all uric acid has been removed by a course of salicylates, soda or potash will fail to increase the excretion of uric acid, and in this case they will also fail to affect the pulse tension and the flow of urine.

The facts about lithia are very interesting, and I find on a reference to my old notes and curves that on a day when no drugs were taken the urinary water was 1280 cc., and there

was a plus excretion of uric acid (1—24). On the following day 25 grs. of the citrate of lithia were taken, and with this there was, as is usual with lithia, a great fall in acidity of the urine, viz., to 38 grs. from 62 grs. on the previous day, but in spite of this uric acid was diminished greatly, having a relation to urea of 1—44. And now mark the result: if an ordinary alkali had been given, as potash or soda, to produce such a fall of acidity, a plus excretion of uric acid would have been the result, the pulse tension would

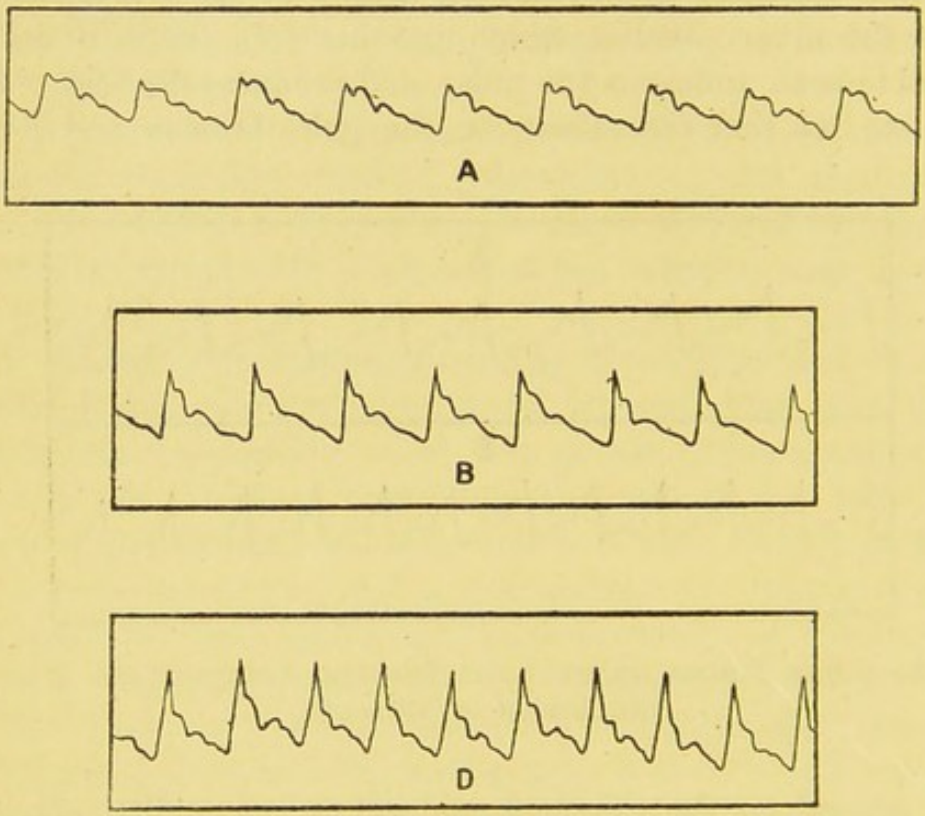

FIG. 23.—(A) HIGH TENSION PULSE OF OPIUM REBOUND. 7.30 A.M. ON THE MORNING AFTER MORPHINE. THREATENING OF HEADACHE; PULSE, 60.
(B) LOW TENSION PULSE OF OPIUM WELL BEING.
(D) LOW TENSION PULSE OF ANTIPYRIN WELL BEING.

have been high and the urine scanty, but lithia, for the reasons given, p. 30, produced retention of uric acid, cleared it out of the blood, and in spite of the rising alkalinity there were relaxed arterioles and a very marked diuresis. The urine of the day before the lithia with a plus excretion of uric acid was 1280 cc., that of the lithia day with a minus excretion of uric acid was 1790 cc. Here again we see that the relaxation of the arterioles

and the diuresis resulting depends not on the greater or less alkalinity, but on the greater or less amount of uric acid in the circulation.

In contrast to lithia see the effect of other alkalies. On March 16th, 1888, no drugs, urine 1410 cc.; on March 17th, pot. bicarb. gr. xxx., urine 1400 cc.; on the 18th, pot. bicarb. gr. xx., sodii bicarb. gr. xx., urine 1170 cc., and with this fall in urinary water there was a plus excretio of uric acid.

Again on May 19th, 1887, with no drugs urinary water was 1670 cc., and uric acid to urea 1—32. On 20th, with 70 grs. of bicarbonate of potash urine was only 1260 cc. and uric acid to urea 1—26, *i.e.*, with a plus excretion of uric acid under alkali the urinary water was reduced, which corresponds with the fact that in the natural plus execretion of uric acid in migraine the urine is scanty and bears out what I have said previously, that the urinary water is inversely as the uric acid excreted along with it.

The action of iron and lead is precisely the same; so long as they diminish the excretion of uric acid they relax the arterioles and produce diuresis, but when their first action comes to an end uric acid is excreted in excess, and there are then high tension, slow pulse and scanty urine, just as in the opium rebound.

All other drugs which diminish the excretion of uric acid produce just the same results; as cocaine (which is almost identical in action with morphine), antipyrin, the nitrites and various salts of the mineral acids, especially sulphates. Strychnia also (possibly indirectly) raises acidity and affects uric acid, and the pulse and urine, like other members of the group, and caffeine the same; the diuresis produced by caffeine is well known, and my results show that it corresponds with a diminished excretion of uric acid, so that its action also is included in my law, and the diuresis produced by uric acid itself has an exactly similar causation. (See p. 65 and 72.)

If now we turn to pathology, we again find a whole series of facts which our knowledge of the effects of uric acid on the arterioles will enable us to explain completely.

There are few clinical facts which are better attested than that having to rise one or more times in the night to pass urine

is a very common symptom in Bright's disease, but it will, I think, presently appear that this is not so much a symptom of Bright's disease as of a condition (high arterial tension), which is very commonly present in Bright's disease.

When a patient tells me that he has to rise one or more times in the night to pass water, I feel sure that he has high tension (provided, of course, there is no local irritation in the urinary passages), but this may or may not be due to Bright's disease.

As we shall see further on (chapter xiii.) the high tension of Bright's disease is almost certainly due to uric acid, that is a patient with Bright's disease suffers from chronic uric-acidæmia, but it is equally certain that a patient may have uricacidæmia without having Bright's disease, hence nocturnal urination does not necessarily imply Bright's disease.

The execretion in my own person on May 8th, previously mentioned, will very well illustrate what I mean. On this day there was marked uricacidæmia in the alkaline tide, and the urine during the day was only 35 cc. per hour, but at night the acidity rose, the uricacidæmia came to an end, and the excretion of water rose to 81 cc. per hour. Now, something of this kind happens in the high tension of Bright's disease every day ; there is chronic uricacidæmia, but this is most marked in the alkaline tide of the morning when the slow pulse is at its slowest, and the hourly excretion of water at its lowest ; it is least marked in the acid tide of the night when the pulse is at its quickest and the hourly excretion of water at its highest ; hence the patient with high tension, whether he has Bright's disease or not, has to rise in the night because he excretes much more water per hour at that time, and in my own case I have, under conditions similar to those of May 8th, been roused up in the early hours of the morning by a distended bladder. Under the opposite conditions eight or nine hours may easily pass without micturition being necessary.

(For a case in which the hourly excretion of urinary water was much greater in the night than in the day in association with slow high tension pulse, see case " Obesity Treated by an exclusively Nitrogenous Diet and copious Libations of Warm Water, by Thomas D. Savill, with remarks on the excretion of uric acid, by Alexander Haig," *Lancet*, vol. ii., 1893, p. 133).

With regard to the slow high tension pulse of Bright's disease, it is not only slowest and of highest tension at those hours (alkaline tide) when the excretion of uric acid is normally greatest, and quickest and of lowest tension in the acid tide of the night, but it is in our power to alter it, to quicken its rate and reduce its tension by the use of any of the drugs which diminish uricacidæmia just as in the case of the temporary uricacidæmia of a headache. Thus, in some cases of Bright's disease, where the pulse was slow, I have been able to nearly double its rate by influencing the uric acid (see fig. 24), and when several years ago there was some writing in the journals about the value of opium in nephritis, and in uræmic convulsions, I tried opium in one or two cases of Bright's disease, and where, in these cases, the pulse was slow, it invariably quickened it and increased the urinary water, and appeared to me to do good, though in cases of nephritis I have generally preferred to use acids to affect the uric acid rather than opium.

It may interest those who have not a laboratory at their door, if I say that the main characters of the high and low tension pulse can be demonstrated by means of a Higginson's syringe, a few feet of soft rubber tube just large enough to fit over the nozzle of the syringe, and a screw clamp. Fill the syringe and tubes with water, and screw up the clamp so that the water can only run out very slowly from the end of the tube; adjust a sphygmograph over the tube between the syringe, which with a muscular hand outside it represents the heart, and the clamp which represents the more or less contracted arterioles. When all is ready set the clockwork of the sphygmograph in motion, and work the syringe regularly by the second hand of a watch. If the clamp is much screwed up you will get a slow diastolic fall, the secondary waves being nearly obliterated. If it is open so that the water passes easily you get a quick diastolic fall with large secondary waves, as in the dicrotic pulse. If the finger is placed over the tube instead of the sphygmograph, you will be able to appreciate the difference between an artery which is full between the beats, and one which is empty.

In epilepsy the pulse is often slow and of high tension just before the fits, and I have suggested that high arterial tension is the actual cause of the fits, and in the case of epilepsy I have shown that this condition of pulse corresponds with an excessive

excretion of uric acid, and probably with more or less marked uricacidæmia. The urine excreted at the time of a fit is also scanty, and of high specific gravity.

In uræmic convulsions I have pointed out Sir W. H. Broadbent's opinion that the high tension is the cause of the fits, and in writing of Bright's disease I shall have to point out that the blood in that disease has been proved to contain excess of uric acid, and that it is easy to explain the fact, so that uræmic fits or the high tension which produces them may be just as in ordinary epilepsy due to uric acid.

Probably the same explanation may be applied to puerperal convulsions, as the fits come at a time, as I have elsewhere said, when some uricacidæmia is almost certainly present (*Brit. Med. Journ.*, Feb., 1889, p. 290).

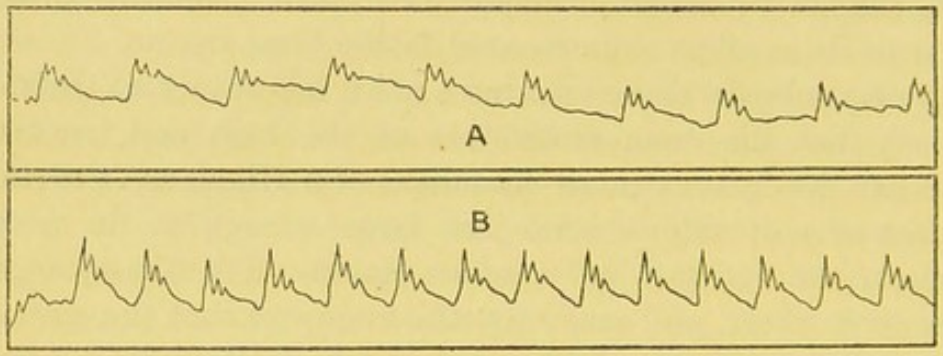

FIG. 24.—(A) HIGH TENSION PULSE OF BRIGHT'S DISEASE, RATE 52.
(B) PULSE OF SAME PATIENT TEN DAYS LATER, RATE 80; TENSION RELAXED BY DRUGS.

In mental depression and melancholia, as we shall see presently, Sir W. H. Broadbent has pointed out that the pulse is often slow and of high tension, while I have shown that these conditions are often associated with an excessive excretion of uric acid, and more or less uricacidæmia, and that they may be relieved or cured by affecting the uric acid.

The fact on which I have laid so much stress above, that the urinary water varies from hour to hour or day to day and in physiology as well as in pathology inversely, as the uric acid excreted along with it, seems to me to afford absolute and irrefragable proof of the action of uric acid on the arterioles.

That the urinary water varies inversely as the uric acid anyone who will trouble to estimate the excreta for a few days can

easily convince himself; and it does so because an excess of uric acid over urea in the urine comes from an excess of uric acid in the blood, and an excess of uric acid in the blood contracts the arterioles and diminishes the excretion of water just as we have seen that digitalis and erythrophlæum do; therefore, contraction of arterioles is directly as the uric acid in the blood (Q.E.D.).

Contraction of arterioles is not directly as any of the drugs used to affect uric acid, as these act quite differently in accordance with the amount of uric acid that is present for them to act upon: thus an alkali given to a gouty person will cause high tension and severe depression; but remove the uric acid beforehand with a salicylate and it will cause none. Lithia produces no depression and allows of a free flow of urine; soda and potash cause depression and scanty urine; they all render the blood more alkaline and the urine less acid; but lithia clears the blood of uric acid, while soda and potash produce uricacidæmia.

I have just said that contraction of the arterioles varies directly as the uric acid in the blood, and pulse rate according to Marey is inversely as arterial tension, which is the result of arteriole contraction; therefore, pulse rate is inversely as the uric acid in the blood.

Now this brings me in contact with a subject about which a good deal has been written, namely, bradycardia, or slow action of the heart; and Prof. Reigel, from whom I have quoted elsewhere, divides bradycardia into physiological and pathological, and a close investigation shows that in all the conditions he speaks of there is uricacidæmia, which contracts the arterioles, and the bradycardia is due to this, in accordance with Marey's law.

In the physiological group come (1) the bradycardia of ten to twelve days after confinement; (2) that of conditions of hunger; (3) that of individual peculiarity.

After confinement, as I have pointed out elsewhere (*British Medical Journal*, Feb. and Nov., 1889), there is almost certain to be uricacidæmia, because there is an interruption of digestive and other functions at the end of a period of active nitrogenous metabolism (pregnancy), and these facts probably explain also the causation of puerperal convulsions.

In certain conditions of hunger, also, there is a fall of acidity and temporary uricacidæmia.

As to individual peculiarity, Prof. Reigel himself suggests that it often means some unrecognised disease.

In the pathological group come bradycardia of

(1) Convalescence from acute disease.
(2) Diseases of digestive organs.
(3) ,, respiratory ,,
(4) ,, circulatory ,,
(5) ,, urinary ,,
(6) Intoxications.
(7) Diseases of blood and general nutrition.
(8) Diseases of nervous system.
(9) Other diseases.

Of (1) Acute diseases and the way in which they bring about uricacidæmia, I shall have to speak very often (see chapter viii.), but I will just mention here that I have no doubt that the relaxed arterioles and dicrotic pulse of fever are due to the clearing of the blood of uric acid by the rising acidity which fever produces. The pulse of fever often much resembles that produced by the nitrites which I have suggested is due to the same cause, a rise of acidity, but it follows from my first principles that a rise of acidity clearing the blood of uric acid causes retention of uric acid, and this retention will be followed, as in the case of opium and other drugs, by a rebound and plus excretion; that is to say, as the fever comes to an end and the acidity falls, the retained uric acid will be dissolved out and flood the blood, we shall have more or less severe uricacidæmia according to the amount retained, and slow high tension pulse (post febrile bradycardia), subnormal temperature, &c., in proportion to it. Hence a knowledge of the effects of uric acid enables us to explain the pulse conditions both in fever and convalescence, and to see that the pulse of the latter is the necessary sequence of that of the former. (See p. 109.)

With regard to changes in the rate and rhythm of the heart, Marey says that while they are often attributed to nervous influences, they are in not a few cases really due to pressure changes in the vessels either of the systemic or the pulmonary circulation (prev. ref., p. 484).

Writers on this post febrile bradycardia have observed that it is often met with in its severe forms in those who before the fever were strong and healthy, and yet in apparent contradiction they go on to attribute the bradycardia to weakness of the heart muscle.

Why should those who were previously strong and healthy have the weakest hearts after a fever? There is no doubt, however, that those who are strong and robust had the largest nitrogenous metabolism both before and during the fever; they would, therefore, store most uric acid and have the most severe uricacidæmia after the fever, and the bradycardia would doubtless be in proportion to this.

As regards the heart, the only necessary quality for the production of bradycardia is that it shall be sufficiently strong to withstand the strain which uricacidæmia, contracted arterioles and high arterial tension put upon it, and this power is, to my mind, much more likely to be met with in those who were previously strong and robust, but if the heart fails before the high tension, we shall get palpitation or a quick, irregular pulse in place of a slow one.

(2) Digestive disturbance generally entails a fall of urea and acidity and uricacidæmia, and this is the common occasioning cause of the uric acid headache.

(3) Respiratory disease may entail deficient oxidation, and that, as I have pointed out in chapter iii., pp. 60-61, means a fall of acidity and uricacidæmia.

(4) Circulatory disease may obviously cause uricacidæmia in several ways.

(5) In urinary diseases, nephritis bulks largely, and of this and its uricacidemia I shall speak in chapter xiii.

(6) Intoxication by lead, alcohol, digitalis, and bile are specially mentioned, and the action of lead and alcohol on uric acid I need not go into again. Digitalis acts in accordance with the same law, and slows the pulse by contracting the arterioles and raising the blood pressure. The disturbances that accompany jaundice are probably sufficient to cause uricacidæmia, and jaundice is not always accompanied by a slow pulse, which points to the action being indirect.

(7) I shall only have to mention anæmia or leucocythæmia in reference to what I say in chapter xii. of the uricacidæmia that occurs in relation to them.

(8) As regards the nervous system I admit that certain central irritation may contract the peripheral arterioles, raise arterial tension, and produce bradycardia, but I believe that disease of the nervous system more often acts indirectly by producing

nausia, vomiting, or gastric disturbance with secondary uric-acidæmia and its resultant bradycardia. (See previous quotation from Marey.)

Under (9) are grouped fatigue, sunstroke, severe pain in various organs, and I should have no difficulty in proving that these may be accompanied by uricacidæmia, and I shall speak of fatigue in connection with the causation of mental depression, chapter viii.

With regard to fatigue I will just remark, in passing, that while drugs which clear the blood of uric acid and promote a free circulation in the nervous and muscular tissues, such as morphine, cocaine, acids, &c., produce, as they are well known to do, feelings of mental well-being and bodily strength, and greatly increase the powers of endurance, it is extremely likely that drugs and physiological or pathological conditions which increase the uric acid in the blood, and so hinder the circulation through these tissues, will produce fatigue, or a condition on which it easily supervenes.

From the causation of bradycardia by uric acid in accordance with Marey's law we pass without difficulty to the causation of angina (see chapter xiv.), and of syncope (see also *Brain, Spring Number*, 1891, p. 88). Acute dilatation of the heart and other effects of high tension and the value of nitrites and mercury in such conditions is easily accounted for. I give here, figure 25, a trace showing an intermission in my own pulse when the heart was labouring against the high tension of uric-acidæmia, and I have suggested that epilepsy may in some cases be due to heart failure from this cause.

An interesting form of syncope is that which occurs during bathing and no doubt accounts for the loss of many lives every year.

Now bathing is commonly indulged in during the morning just at the hours of physiological uricacidæmia, and when to this is added contraction of all the surface vessels by cold it is little wonder that the heart is sometimes overpowered, and that powerful contraction of arterioles may bring the heart to a dead stop is acknowledged by Sir W. H. Broadbent ("Pulse," p. 153).

As regards my own pulse, I look upon a fluttering, imperfect systole, or a dropped beat, as in figure 25, as conclusive evidence

of high tension. I have many hundreds of traces of my own pulse, but none show these conditions without accompanying (causative) high tension, and I have often produced this condition or removed it in myself and others.

With reference to some of the points just mentioned it is interesting to notice that Marey says that the pulse in typhoid fever is, first of all, soft and dicrotic, and later on the approach of convalescence shows more or less high tension, and he goes on, "L'apparition du triple rebondissement (= w pulse of high tension as in trace A, fig. 25) est un caractere important de l'approache de la convalescence; nous le rencontrerons a la fin des autres maladies febriles. Au moment de la convalescence le pouls presente parfois aussi un peu d'irregularité." (Prev. ref., p. 569.) That is to say, during high fever there is retention of

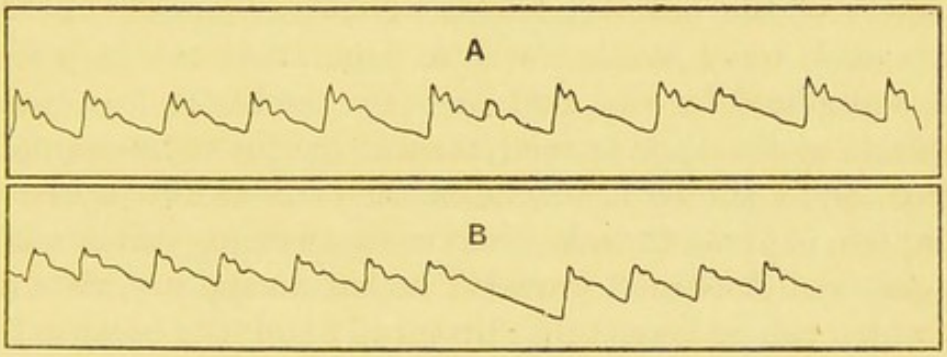

FIG. 25.—PULSES OF HIGH TENSION. (A) FALTERING, RATE 58; (B) INTERMITTENT.

uric acid, and little or none in the blood, but as the temperature begins to fall the alkalinity of the blood increases, it soon dissolves a considerable quantity of uric acid which produces high arterial tension, and the heart often flutters or falters as the pressure rises.

Again, with regard to alcohol, Marey says, "Certains agents l'alcool, par example, mettent la circulation dans un etat analogue à celui de la fievre typhoide; le pouls de l'ivresse à moins qu'elle ne soit accompagnée de troubles gastriques presente a un haut degré le dicrotisme." (Prev. ref., p. 570.) Why this exception in the case of gastric troubles? Marey appears from the context to attribute it to irritation of the abdominal sympathetic, but I am only following his own rule with regard to heart rhythm just quoted on p. 106, in suggesting that the absence of dicrotism in gas-

tric trouble is really due to uric acid, and the intra-vascular pressure changes it produces, and not directly to the nervous system ; for gastric upset means that there is diminished absorption of alcohol, or the acids so frequently ingested along with it, diminished absorption also of food with its resulting diminished formation of urea and acids, and the result of all this is an increase in the alkalinity of the blood, which at once takes up an increased quantity of uric acid, and this contracts the vessels and prevents more or less completely the dicrotism which would otherwise be produced by alcohol and acids.

Marey then goes on to point out that a feeble pulse becoming almost imperceptible in the radial ; but presenting the pulse trace of extremely high tension, is the pulse of *mal de mer*, and of nausea or vomiting. I would point out that in sea-sickness there is very commonly a headache, which has, I believe, all the characters of the ordinary bilious headache (migraine) produced by uric acid, and I see no reason to doubt that the high tension pulse is produced by uric acid, and that the headache represents the effects of the high arterial tension on the intra-cranial circulation, and a similar headache can be produced in anyone who, like myself, is prone to suffer from it, by anything which will produce gastric disturbance, provided he has a supply of urate in his body which can be taken up by his blood ; and it is because I have not this supply of urate that I now have immunity from headache.

On the other hand, where there is contraction of arterioles, but the heart is powerful, perhaps hypertrophied, and refuses to give way, dilate or furnish imperfect systoles, tension will rise to a dangerous extent, and especially where the vessels are already degenerate hæmorrhage will occur.

This may be comparatively harmless in the form of epistaxis or a more or less profuse hæmoptysis (and I have elsewhere[1] suggested that what the late Sir Andrew Clark has written about as "arthritic hæmoptysis" may be due to uricacidæmia and its effects on the the circulation) or may be fatal and deadly as a hæmorrhage in the brain.

I am now collecting records of cases of syncope, hæmorrhage, &c., with the object of finding out whether a majority of them occur at the times of physiological uricacidæmia, the "alkaline

[1] *Wood's Medical and Surgical Monographs*, February, 1890, p 359.

tides" of the morning or afternoon, pathological exaggerations of which may satisfactorily account for their causation.

As to the arteries themselves, high tension means a certain amount of strain, and strain is supposed to lead to degeneration of structure. Then it is at least probable that the vasa vasorum are among the vessels affected by the urate, and so nutrition is soon involved, and as effects of both causes we have degeneration, atheroma, and other changes. The same argument applies to the heart. We get first hypertrophy and then degeneration, or we get sudden syncope or angina occurring in the alkaline tide, and due to a contraction of arterioles for which it is unprepared, the fluttering heart of uric acid headache or epilepsy being minor stages of the same thing. I shall have more to say about syncope and angina in chapters viii. and xiv., but its causation by the contracted arterioles of uricacidæmia follows directly from what I have said about fig. 25, and this explains completely its occurrence after fevers, influenza, &c., or in association with gout, dyspepsia and glycosuria; it also explains the relief afforded by mercury, morphine and the nitrites, for all these drugs clear the blood of uric acid. (For some interesting points in favour of this causation of angina, see article by Professor T. J. Mays, of Philadelphia, "International Clinics," 1893.) Several of my epileptic patients have told me that they often shivered with cold (contraction of arterioles of the skin) or felt a fluttering in their throat (sign of a single non-habitual intermission of the heart) just before a fit comes on.

As to the skin, there is the cold skin of migraine passing through all stages of severity up to Raynaud's disease, or various interference with function and nutrition, producing urticaria, erythema, &c., and where the skin has long been under the power of urates, perhaps leading to that atrophy and loss of structure described by Semmola (see chapter xiii.) as being present in Bright's disease.

In the brain we may have slow circulation or stasis as in headache, vertigo, epilepsy, and mental depression, and possibly œdema as in uræmia, all due to the effects of urates on its circulation, not to mention softening and hæmorrhage from organic arterial changes having similar origin.

In the cord, we have no doubt, similar functional and nutritional changes, and in the peripheral nerves, if I mistake not, neuritis and perineuritis, also due to vascular conditions produced by urates (see Charcot in *Prog. Med.*, vol. ii., 1890, p. 83-102 and

Buzzard, *Lancet*, vol. ii., 1893, p. 1233), and toxic neuritis may represent the effects of the drug on urates. Then again there are many interesting eye symptoms which are more or less closely related to high arterial tension; for not only has stasis or thrombosis in the vessels of the retina been seen during attacks of migraine (see *Ophthalmic Review*, March, 1890, paper by Mr. Stanford Morton), but Dr. Lauder Brunton (*British Medical Journal*, vol. i., 1892, p. 7) and the late Dr. J. Anderson and others have noticed the connection between intra-ocular tension and high arterial tension.

It seems probable that in the eye we have a similar set of forces to those which bring about stasis and hyperæmia in the cranial circulation and that the pathology of glaucoma closely parallels that of headache or mental depression, and I have myself seen cases in which eye pain apparently related to glaucoma was immediately relieved by a drug which reduced arterial tension. Of the kidneys I have already said much, and of the way in which urates diminish the excretion of water and retain it in the body; one interesting effect of this is probably the œdema of eyelids, which has been noticed by several observers as occurring in migraine. I had my attention recently drawn to it by Dr. Gogarty, of Canterbury. (See also *British Medical Journal*, i., 88, p. 1,006, and compare anasarca case in chapter xiii.)

I have no doubt that the nutrition of the kidneys, liver and other organs is eventually affected by the vascular changes which urates bring about in their parenchyma; the chief changes being an alternation of anæmia with hyperæmia, these being often intensified by the more serious secondary effects of the urates on the heart and general circulation.

The effects on the muscles can scarcely be less important than that on the skin and other organs, and when their vessels are contracted by urates no doubt the nutrition of the muscles is more or less seriously interfered with, and as they, like the liver, are important organs of metabolism, there can be little doubt that general nutritional changes may be seriously interfered with when their circulation is impeded: I shall have to suggest that in glycosuria, and albuminuria when temporary and not associated with actual kidney lesion, we may see results of such metabolic disturbance. Whenever arterial tension is high, and it is relaxed by giving an acid, I have noticed that there is almost certain to

be a rise of urea; I have suggested that this rise of urea is due to an increased formation of urea, when the metabolic processes in the liver, muscles, &c., are set free from the restraining influence of uricacidæmia.

It is a simple matter to alter the tension and rate of the pulse in either direction, but as in all the other effects of urates of which I have written, it is much simpler in physiological than in pathological conditions, and this difference must be kept in mind.

A large number of workers, both in England and abroad, have devoted their energies to the investigation of high arterial tension, the conditions under which it is met with, its origin, and its results. A considerable number of them agree in attributing it to some condition very commonly found along with rheumatism, gout, and allied diseases, and also in describing a large number of the other diseases I mention in this volume, as its more or less direct effects.

The late Dr. King Chambers appears to have regarded vascular tension as due to the presence of waste products in the blood, and treated the condition by diet, I may say that he took a great interest in the early stages of my research, and wrote me several letters containing points of great interest; among others he mentions a case of epilepsy, which rather to his surprise was apparently cured by diet. Dr. Chambers ordered his patient to reduce his meat and beer, but he being young and enthusiastic went beyond his instructions, and left off both entirely; eighteen years afterwards he had never had another fit; I shall have to relate a somewhat similar case in chapter vii.

If my facts have been truly observed and my deductions are sound, I go but one step further, and assert that a very common cause of high arterial tension is excess of urate in the blood, and that this explains the well-known connections between gout and its allies on the one hand and those diseases which are due to high tension on the other, as well as a considerable series of physiological and pathological facts of scarcely less importance.

Where there is bradycardia, that is, where the heart does not complete more than sixty cycles in a minute, where the radial artery rolled under the points of three fingers feels full between the beats, and the pulse gives a trace as in fig. 26, where the first sound of the heart is long, and the second sound both at the apex and over the aortic area is loud, and where also the skin

and extremities tend to get easily cold, and the urine and other secretions tend to be scanty, there can be very little doubt about the presence of high arterial tension, and when there is high arterial tension, and there is reason to believe that it is doing harm, the obvious indication is to reduce it, and this may be done temporarily by drugs, such as the nitrites, mercury or the iodides, or more permanently by such diet as will keep the blood relatively clear of uric acid.

If there is hæmorrhage, we must enquire first of all whether it comes from the arteries or from the capillaries and veins, whether it comes from the distal or proximal side of our screw clamp. If from the capillaries on the distal side of the clamp the obvious indication is to screw up the clamp, and this is, I think, the way in which ergot stops such hæmorrhage as that from the uterus, though even here high arterial tension has some influence in increasing the flow of blood. On the other hand, when the hæmorrhage is arterial, as from an eroded vessel in the stomach or the lungs, or a ruptured vessel in the brain, the indication is to lower arterial tension by relaxing the screw clamp as much as possible; and this is, I believe, the way in which such drugs as opium and lead relieve; as their first action is to clear the blood of uric acid and relax the arterioles; and we must beware that their second action or rebound, in which the arterioles are contracted (see fig. 23), does not occur too soon, *i.e.*, before the vessel is securely plugged, or we shall have a return of the hæmorrhage.

CHAPTER VI.

Headache.

The headache which I have ventured to call "the Uric Acid Headache" from the result of my investigations as to its causation, is, I believe, the same thing as migraine, megrim, sick or bilious headache, for an account of the history, symptoms and relationships of which to other diseases we owe so much to Dr. Liveing.

And, as before mentioned, it was his most interesting work which turned my attention to the urine as a possible source of information as to the gouty relationships, and so as to the causation of the headache.

The points about this headache which, to my mind, best serve to distinguish it from others are (1) its periodicity; it occurs once in a week, fortnight, month or longer period, for many years, or for the whole life of a patient; it tends to be more frequent and severe in the spring and early summer, and in women it almost always attends the menstrual epoch; when present it tends to be worst at those hours of the day in which the excretion of uric acid is normally greatest, viz., in the alkaline tide of the morning, and during another period of low acidity, generally from 3—6 p.m. (See fig. 20.) (2) Its duration is generally under twenty-four hours, though in exceptional cases it may last for forty-eight hours; a patient goes to bed with a more or less severe headache, and wakes in the morning free from it. This short duration is of great diagnostic importance in distinguishing it from the more continuous headaches such as those due to neuralgia or intracranial disease, which often last for days or weeks with little or no alteration. The uric acid headache is due to the passage of an excess of uric acid through the blood; but apart from organic disease this (uricacidæmia) can for obvious reasons only last a

few hours, the uric acid is all excreted and the headache will pass away with it.

As noted by Liveing and others the pulse is slow and of high tension (see fig. 26), the surface and extremities are cold, and the temperature even in the axilla is subnormal. (Some observers have noted pulses of 48 and 52 during the attack. See "Fagge's Medicine," Ed. ii., vol. i. p. 784).

The tongue may be clean or slightly furred, the appetite may be fair but is often irregular, a feeling of emptiness and ravenous hunger being quickly replaced by a feeling of distension and satiety; in fact there are signs of dyspepsia, though they are often slight. When the headache is severe there may be nausea or vomiting; but these are generally late symptoms, and are absent or little marked when the headache first comes on.

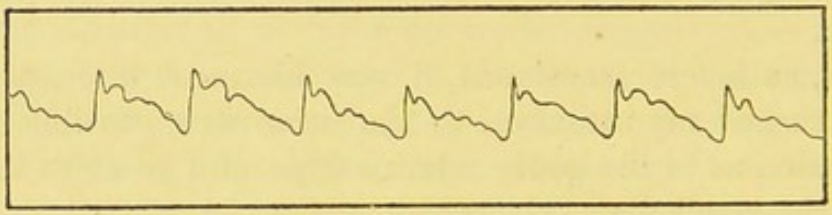

FIG. 26.—HIGH TENSION PULSE OF A URIC ACID HEADACHE. RATE 57.

The bowels may be regular and the motions natural; but, commonly, like the appetite, they are a little irregular, either slightly relaxed or slightly constipated.

The urine during the attack is scanty and of high colour and sp. grav.; thus in the attack it may not exceed 30—40 cc. in the hour; after the attack, and especially just as it passes off, it may run up to 100 or 150 cc.—or more—in the same period.

There is often a family history of headache of the same type, or of epilepsy together with gout and rheumatism, and not very rarely phthisis; chronic nephritis and cerebral hæmorrhage should also, I think, be added to the list of family complaints.

When a headache has a majority of these characteristics well marked there is rarely much difficulty as to the diagnosis; but there are several important ways in which we can put our diagnosis to the test.

If the scanty urine of the headache is carefully separated from that passed before and after, it will be found to contain a relative

excess of uric acid having a relation to urea varying in different cases from 1—25 to as much as 1—12 or 1—15, and generally speaking, the greater the relative excess of uric acid and the greater its absolute excretion per hour the more severe the headache; thus with a headache I find .6 gr. of uric acid per hour and upwards, and when I have removed the headache by acids the excretion falls to .45 gr. per hour or less; the urinary water undergoing, as before mentioned, an inverse change. Fig. 27 shows the excretion of uric acid and urea on nine consecutive days, on one of which there was a severe headache lasting nearly the whole twenty-four hours. The way in which the uric acid runs up apart from the urea is well shown, and it is also seen that the uric acid was below the urea on each of the six days preceding the headache; and if we add together the amounts by which uric acid fell short of urea on these days it shows that there was a total retention of about 4½ grs., and this is almost exactly the amount by which uric acid exceeded urea on the day of headache. Then again, from December 28th to January 1st, urea fell steadily, and with this fall no doubt acidity would fall also to a corresponding extent, and the result of this sooner or later was sure to be a plus excretion of urate and a headache.

This figure also well illustrates what occurs after several good dinners or any other causes that run up the formation of uric acid and urea. As the urea and acidity goes up the patient feels very well and thinks he is all the better for them, because uric acid is being retained; but as urea and acidity fall, as they are bound to do, the stored uric acid is bound to come out, and then he will have headache, mental depression, or other disorder as the result of his indiscretion. (See fig. 16, and *Journal of Physiology*, vol. xv., plate x., fig. 4.)

It is evident, therefore, that we can not only explain every feature in the causation of this headache, but can imitate nature, control uric acid and urea, and produce the disorder at pleasure.

My readers can also see at a glance the effects of diet in these troubles, for if my urea level (that is, formation) had been at 350 grs. or below, as it is now, instead of 400 or 500 grs. as in this figure, the urate excretion on the day of headache would only have reached 12 or 13 grs. in place of 16, and the headache which depends on the absolute quantity in the blood would have been less severe.

In illustration of some of these points I will now explain the way in which a slight or severe headache may be brought about intentionally or otherwise.

And first let us have an intentional headache: our problem is to produce a fluctuation in the excretion of uric acid so that 4 or 5 grs. shall be prevented from passing out in the natural way, shall be retained in some part of the body, be dissolved out and again enter the blood a few hours later, and in passing through it produce headache and other symptoms.

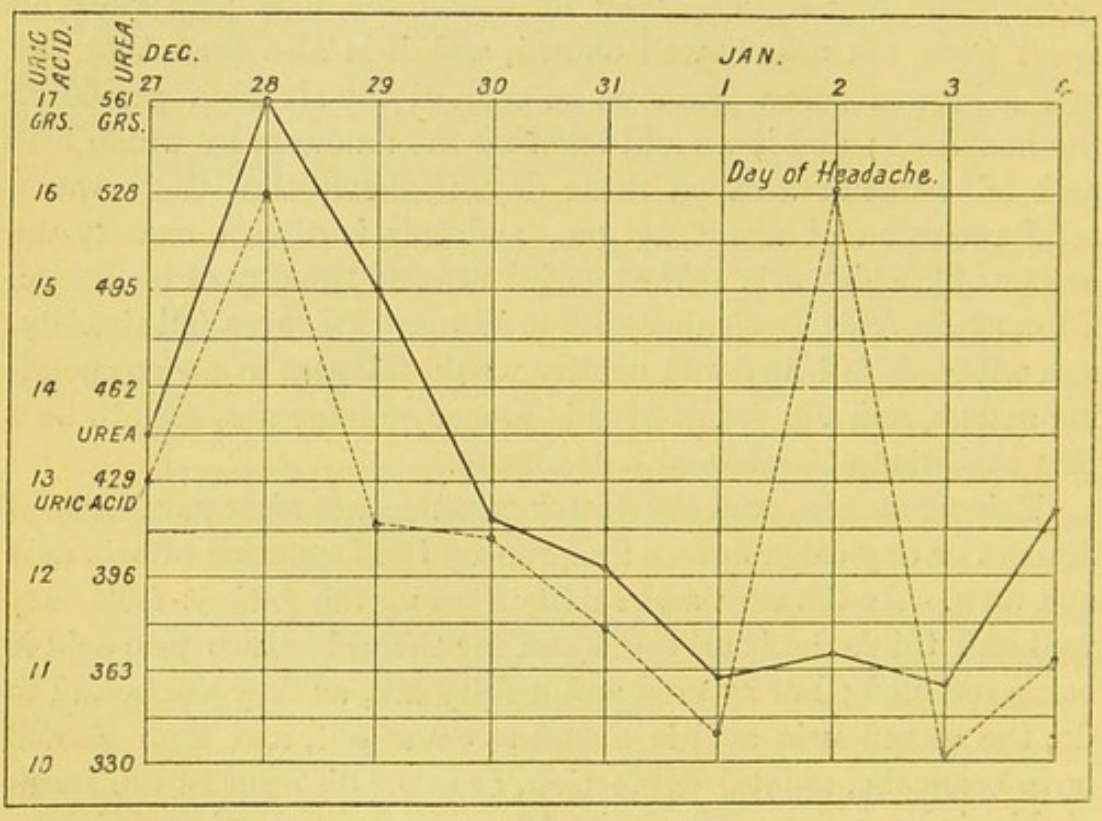

FIG. 27.—CURVES SHOWING THE EXCRETION OF URIC ACID AND UREA, BEFORE DURING, AND AFTER A HEADACHE.—From *Med. Chi. Trans.*

As above mentioned, the largest excretion of uric acid in the twenty-four hours takes place in the alkaline tide of the morning, and one of the simplest ways of producing a fluctuation in excretion is to interfere with the natural plus excretion of the alkaline tide.

By giving any of the drugs in the list of those which diminish the excretion of uric acid such as acids, opium, antipyrin, mercury (see fig. 11), either before, with, or soon after breakfast,

a certain amount of uric acid will be held back from excretion (see curves) during the morning; but if no more of the drug is given the acidity will fall, as it naturally does after lunch, between the hours of 3 and 6 p.m., and then the uric acid kept back in the morning will be taken up in the blood and begin to pass out by the kidney, and more or less headache and other symptoms will result.

Another very simple way is to take a little opium with or after lunch; this will raise acidity and interfere with the uric acid excretion of the afternoon alkaline tide (3—6 p.m.) and hold back some uric acid; then next day there is sure to be some plus excretion of uric acid with slow high tension pulse, headache, &c., in the early alkaline tide of the morning.

It must clearly be understood that I am here speaking of physiological conditions, and of the action of drugs on uric acid in persons who are in perfect health; where there is functional disturbance, and still more where there is organic disease, the conditions are much more complex.

Suppose only that a patient has dyspepsia and fails to absorb his food, acidity and urea both get less and less, and a lowered acidity of the urine may continue the whole day and a plus excretion of uric acid will result for the same period, or till, as the gastric conditions improve, food is again absorbed, the urea and acidity curves rise and the excessive excretion of uric acid is put an end to.

And these considerations explain what is seen every day as to the effects of diet in preventing or producing a uric acid headache: if, say, a patient has a slight headache but is still able to take food well, a good dinner with a liberal allowance of wine may remove his headache and make him feel much better because it (especially the wine) raises the acidity and clears the blood of uric acid; and this rise of acidity will commonly continue next morning, and he will feel bright and well next day also; but if he eats and drinks at this dinner not wisely but too well—if he takes so much both of food and of wine as to overpower gastric digestion—the effect will be very different, digestion will cease, and be replaced by nausea and vomiting, and with this urea and acidity will fall and the uric acid will soon be again in excess in the blood, and a severe headache will occur next morning in place of well-being and brightness which would have been present if the

stomach had not been upset; the second day after a dinner, however, urea and acidity will fall, and then the headache will return unless the uric acid be in the meantime removed by a few doses of a salicylate, which is the way in which I commonly ward off the evil effects of a dinner.

Again, suppose that we have organic disease of the stomach, such as ulcer or new growth, the fall of urea and acidity will be constant and progressive. Suppose that urea falls from 500 grs. to-day gradually to 400, 300, and even 250 grs. in twenty-four hours, the acidity in its relation 1—6 would suffer a corresponding diminution, and the excretion of uric acid would be constantly large, and this state of things would go on till all the stores of uric acid in the body were exhausted, or till something occurred to raise the acidity.

Hence it comes about that a patient slowly dying of wasting disease will excrete for weeks and months an excess of uric acid (some have supposed that the excess was a formation, but I have given my reasons for refusing to credit this explanation, pp. 72-76). If the urine is examined, uric acid will be found constantly above its normal relation to urea—1—33 or 1—35—and this will continue so long as the patient has any uric acid in his body which can be got into solution.

Hence it comes about that in patients who die after weeks and months of wasting disease we find only erosion of joint cartilages but no urates; we should have found the urates in the urine if we had looked for them at any time in the last six weeks, or attention may be called to the excessive excretion by the occurrence of gravel or calculus, but if the same patient had been killed six months ago by acute disease (as pneumonia) we should probably have found them *in situ*, all the erosions being filled and plastered with urate, because during the high acidity of the acute fever there had been no alkali to wash them out.

We can now see that those who speak of erosion of joints without urate deposit as "rheumatoid," and the same erosion with urates as "gout," are endeavouring to make two diseases out of different stages of the same process.

But to return to the causation of headache. If a patient has chronic wasting disease none of the drugs in our list will be able to stop the plus excretion of uric acid: acids, opium, antipyrin—all will alike be overpowered by the flood of alkali; or

where the disease is only functional our drugs may still fail to effect a cure, either because the functions of the stomach are too much upset to permit of their being absorbed, or because, after more or less absoption has gone on, the acids are overpowered by the action of the causes that increase alkalinity. In the case of opium, which, I believe, raises acidity by acting on the intestines, delaying peristalsis and increasing absorption, it is obvious that extensive ulceration may produce so much diarrhœa that only a very large dose of the drug will have any effect.

Under these or similar conditions almost any drug in our list, or several combined, will fail to check the plus excretion of uric acid, or to remove the symptoms which are due to its excess in the blood.

In the above cases of very chronic plus excretion of uric acid the excess is not generally very great, and though the presence of uric acid in the blood is constant, the quantity may not be enough to produce a distinct headache, except now and then for a few hours; but the patient suffers continually from some minor signs of uricacidæmia, of which we shall speak presently.

But, speaking generally, and bearing in mind the above causes of failure, a uric acid headache, accompanied by a plus excretion of uric acid, can be cured within an hour or an hour and a-half by anything that will raise the acidity of the urine and stop the plus excretion of uric acid, and if in any given case we fail to cure the headache we shall find, if we examine it, that we have also failed to raise the acidity of the urine, and stop the plus excretion of uric acid.

We can now explain all the main symptoms and characters of this headache, and first its periodicity: being, as I have said, due to a fluctuation in the excretion of uric acid, the first stage of the fluctuation is a holding back or retention of urate in the body, and during this process there will be little or no urate in the blood, and no headache; on the contrary, the signs will be those of absence of uric acid from the blood, just such as are produced in the first stage action of opium, mercury, cocaine, lead, zinc, acids, &c. The patient will feel more than usually bright, happy, cheerful, and energetic, and there will be no sign whatever of headache; and it depends upon

the length of time occupied by this process of retention how long an interval will be interposed between successive headaches.

On my old meat (ordinary) diet I used to have a headache once in seven to ten days, that is to say, in five to seven days I had accumulated sufficient uric acid to produce another excessive excretion; on my present diet, with an excretion of only about 350 grains of urea per day, and a correspondingly low acidity, I not only form less uric acid absolutely—though still in the same relation to urea—but as acidity falls with urea, nearly all the uric acid I form is at once excreted, and only very occasionally, and at long intervals, or after some excess in nitrogeneous food, do I accumulate enough in my body to produce a headache as it passes through the blood.

Here, again, I must remark that I am speaking of physiological conditions, for, as we shall see later on in pathological conditions, such as nephritis, the problem of uric acid excretion is much more complex.

The onset of a headache is often preceded by a period of more than usual mental brilliancy and well being, thus corresponding with the fluctuation of uric acid excretion which precedes the attack in nature, just as it does when an attack of headache is produced in one of the ways above mentioned. Exactly the same thing has been noticed to occur before the fit of epilepsy, and as we shall see, it is probably due to the same cause.

The relation of headache to menstruation in females is also easily explained, for menstruation is almost always a cause of some little general disturbance of function which often specially affects the digestive organs, so that food is taken badly or badly digested, and exercise is generally deficient. Several of these causes combined bring about some failure of nutrition with a fall of urea and a corresponding fall of acidity, and this is the signal for any uric acid that is on store to be got into solution and flood the blood, hence menstruation is commonly accompanied by a lowered acidity, a plus excretion of uric acid, and the effects of its excess in the blood, such as the slow high tension pulse noted by Sir W. H. Broadbent, and mental depression, of which I shall speak later; and if there is much uric acid on store, more or less severe headache or an epileptic fit.

The reasons why the headache is worst at the hours of normal plus excretion of uric acid—that is, in the periods of low acidity after breakfast and lunch—are now, I hope, too obvious to need further mention. As a rule, and when the kidneys are normal, the five or six grains of uric acid which occasion a headache by their passage through the blood are all excreted in a few hours, and the headache subsides, this explaining its usual short duration. But I have seen several cases in which the attacks of migraine which had been in attendance for years, had suddenly become more frequent, severe, and prolonged, and in these cases further investigation has proved that Bright's disease had supervened, and that an organic cause of uric acid retention had been added to the original functional one. (See chapter xiii.)

As regards the causation of the headache, the effect which, as we shall see presently, uric acid exerts on all the vessels of the body is closely allied to that which, occurring locally, has been supposed to be the cause of the pain. Thus it has been suggested by Du Bois Reymond and others, quoted by Liveing (p. 295 *et seq.*), that the headache is due to irritation of the vaso-motor nerves in the region of the cervical sympathetic giving rise to contraction of vessels in certain areas, followed by dilatation and congestion, which produces pain. Again, Dr. Brunton (*St. Bartholomew's Hospital Reports*, vol. xix., p. 333) has suggested that the proximal ends of certain vessels are dilated, while the distal ends are contracted, and that the impact of the blood against the contracted extremity produces pain. I think, however, that the effects of uric acid in contracting the peripheral vessels and producing high arterial tension, and the further effects of this high arterial tension on the intracranial circulation will give us a much better explanation of the causation of the headache than any more or less hypothetical irritation of the cervical sympathetic.

Taking it for granted, then, after what has been said that an excess of uric acid in the blood does contract the arterioles and capillaries, and cause high arterial tension, the researches of Professor Grashey, which I have quoted at length in *Brain*, Spring and Summer Number, 1893, show that when arterial tension rises above a certain point, the pressure in the closed cavity of the skull becomes so great that the veins are compressed

and begin to vibrate, the blood stream through them being greatly hindered, and from this results more or less stasis and hyperæmia in the veins and capillaries behind the point of compression, with general excess of pressure in the cranial cavity.

But the process does not stop here, for Professor Grashey further suggests that as the cerebro-spinal fluid comes from the blood the above condition of stasis and hyperæmia may bring about an increase in its quantity, and so still further increase the intra-cranial pressure.

It appears to me that such a general increase of pressure acting within the unyielding membranes of the brain may account for the pain of headache, in so far as it is bilateral, and that where it is unilateral, or apparently affecting chiefly the distribution of a single nerve, there may be some œdema affecting specially the sheath of that nerve, and due to the changes in the circulation, just as the more general increase of cerebro-spinal fluid may be due to it. And we may probably account in the same way for the paralysis or paresis of certain nerves which sometimes occurs contemporaneously with a migraine (see *Lancet*, vol. ii., 1893, p. 139), and stasis or thrombosis which would probably produce œdema and pressure have been actually observed taking place in the vessels of the retina during an attack of megrim. (See article by Mr. Stanford Morton, *Ophthalmic Review*, March, 1890.)

With regard to the causation of the uric acid headache, I have noticed in my own case a fact of some interest, namely, that when the pain is severe and situated, as is often the case in my attacks, in the centre of the occiput (? neuchalgia of Dr. Burnett, see chapter viii.), sitting with the head bent back so that the face looks vertically upwards will greatly mitigate the throbbing pain, and it has occurred to me that this position may in some way interfere with the increased pressure of arterial blood that corresponds to each throb. Speaking generally, the vertical position is the only one which is bearable in migraine; when I have an attack I am obliged to sit vertically upright against the back of my bed and slide gradually down into the usual recumbent position as the pain moderates; then again, stooping makes even a slight headache unbearably severe and the effects of position on intra-arterial pressure suffice to explain these facts, for Marey says: "Dans l'attitude verticale

un animal aura donc une pression manometrique plus faible a la carotide que la femorale et surtout qua la metatarsienne." (" La Circulation du Sang," p. 192).

The fact that compression of the carotid has often been used to relieve the pain of the headache tells in the same direction. (See Dr. Liveing, " Megrim and Sick Headache," pp. 276-7.)

Exercise again affects the head pain in accordance with its effect on intra-arterial pressure: thus the first effect of muscular exertion is to raise arterial tension and make the headache worse; but if the exercise is persevered in to the extent of producing general relaxation of the vessels in the muscles, with warm and perspiring skin, this general dilatation of vessels brings about a fall of arterial tension, and the headache departs, and the patient is again able to take a cheerful view of things.

Vertigo is one of the most interesting of the occasional results of high tension, and as its causation is probably exactly parallel to that of headache and epilepsy, it throws an important side light on their origin.

Murchison classed vertigo among the disorders associated with lithæmia, and Dr. Buzzard (" On Vertigo of Bulbar Origin," *Lancet*, vol. i., 1890, p. 179) points out that a gouty history is very common, and that salicylate of soda is useful in treatment, a fact which he explains by reference to my researches on the action of this drug on uric acid.

In so far as vertigo is "of bulbar origin," I take it that it is the exact parallel of uric acid headache or of epilepsy, and that the high arterial tension and consequent intra-cranial pressure which produces the latter may produce also the former trouble; and, indeed, I have had several cases of vertigo in patients with high arterial tension in which the reduction of tension has effected great improvement or cure of the disorder.

It is evident, then, that all that has been said about the causation of headache or that remains to be said about its treatment will apply also to vertigo.

Dr. Buzzard (previous reference) mentions that these attacks may be followed by a large discharge of colourless urine. Here again we have an exact parallel with epilepsy and migraine, and the causation of the symptom I have previously gone into.

I have myself had one or two attacks of temporary vertigo, and these came in the morning at a time when arterial tension

is generally high and the uric acid in temporary excess in the blood, and I looked upon it as a variation of my migraine with which, as regards time of onset and attendant symptoms, it corresponded.

Dr. Buzzard suggests that this vertigo may be due to an affection of the bulb near the origin of the auditory nerve, and signs are not wanting, along with the headache, mental depression and other symptoms of uricacidæmia, of some slight functional derangement in this region, for I have several times pointed out (*Brain*, 1891, and elsewhere) that with these signs of uricacidæmia a certain amount of aphasia with forgetfulness of names, &c., is very commonly associated, and Dr. Bastian (*Lancet*, vol. i., 1890, p. 1164) says: "Thus, when there is a slight lowering of functional activity in the auditory centre we have produced a slight amnesia, with forgetfulness of names of persons and things, the centre not being sufficiently active in this condition to respond to some volitional and associational incitations," and I would remark that in uricacidæmia not a few other centres on which activity of mind and body depend are in a similar condition of lowered functional activity.

Now, a certain amount of this amnesia is one of the most common accompaniments of the headache and mental depression which are due to uricacidæmia, and the centre which, according to Dr. Bastian, is affected cannot be very far from that to which Dr. Buzzard attributes vertigo.

And speaking of similar conditions, Sir W. H. Broadbent says (*Pulse*, p. 249): "There may, for example, be a fugitive aphasia or amblyopia or hemiopia, which are easily explained by stasis or ischæmia in certain vascular areas, but incomprehensible as the results of a poison circulating everywhere through the brain," which I should translate by saying that uric acid, by its effects on the vessels, produces the "stasis or ischæmia," which is the cause of the symptoms in these and similar conditions. The whole brain, and for that matter the whole body, is affected in much the same way, but certain parts, possibly owing to local conditions of anatomy, function or nutrition, are specially affected and give rise to special symptoms.

An interesting case of periodic stammering, having probably an identical pathology with several of the above-mentioned con-

ditions, is recorded in the *British Medical Journal*, vol. ii., 1893, p. 1311, and I have often noticed that stammerers are decidedly worse when they are a little out of sorts, which is generally equivalent to the presence of more or less uricacidæmia.

Hence it is only those people who have these anatomical or physiological peculiarities who suffer from headache, epilepsy, or vertigo, as the effects of uricacidæmia, while others with as much uric acid may almost entirely escape. As regards migraine I have suggested (*Brain*, 1893, p. 250) that the possession of large arteries of supply may render some more liable than others to suffer from the intra-cranial effects of high arterial tension; this in part accounting for the fact that migraine is more common among those who work with their brains than among those who work with their muscles.

The relation of this headache to gout is very interesting, and can be easily explained, and Dr. Liveing, Sir A. Garrod and others have recorded cases in which severe headaches of this kind unexpectedly cleared up on the supervention of an attack of gout, sometimes the first attack in the toe.

Now nothing can be more simple than the explanation of these facts. The urate cannot be in two places at once, and when local injury, plus rise of acidity, causes it to be precipitated on the toe joint, the blood is more or less quickly cleared of the excess it had previously contained; hence the headache, slow high tension pulse, cold surface and extremities, mental depression and scanty urine vanish, and pain and inflammation in one or more joints, with low tension pulse, relaxed arterioles, and a certain amount of fever take their place, and with these, even in spite of some pain, the mental condition is more placid and the urine more profuse.

So far as my experience goes patients generally have headaches early in life and gout later, but not the two together, though patients with well-marked gout may occasionally have severe headaches.

The headache occurs when the conditions tending to the plus excretion of uric acid predominate; the gout attacks occur when the conditions tending to its retention and accumulation predominate. Once urates are extensively deposited in joints they tend to go on accumulating there, so that the blood is kept pretty free, so long as there is no marked and continued

fall of acidity ; but when the patient becomes old and feeble, acidity falls greatly, and the process is reversed ; there is no gout but an excessive excretion of urate, and the signs of uric-acidæmia, headache, depression, slow pulse, &c., are severe and well marked. And it is no very difficult matter to imitate nature, and produce either gouty arthritis on the one hand, or uricacidæmia and headache on the other.

Depending as this headache appears to do on the intra-cranial effects of high arterial tension, it seems evident that anything which lowers arterial tension will do good and make the headache less frequent and less severe.

Now arterial tension varies, as we have seen, chiefly with two factors : (1) the contraction of the arterioles and capillaries, and (2) the power of the left ventricle of the heart to overcome the intra-arterial pressure at each systole.

Therefore, arterial tension can be reduced by two things, namely, (1) anything that will relax the arterioles and capillaries about which so much has already been said, and (2) anything that will weaken the left ventricle and prevent it discharging the whole of its contents into the aorta at each systole.

It is obvious then that not only will all drugs and diet which reduce the uric acid passing into the blood or directly clear it out of the blood do good by allowing the arterioles and capillaries to relax, but drugs or conditions which tend to weaken the left ventricle of the heart will also prevent or relieve the headache by reducing arterial tension. And the drugs which are classed as depressomotors may, I think, reduce arterial tension in this way, partly by reducing the power of the muscles in the walls of the arterioles, and partly by a similar depression of the heart muscle. Now such drugs as tobacco, ipecacuanha and antimony may very probably act in this way, and it is interesting to note that Dr. Liveing records (prev. ref.) that some of them have been used with good effect in migraine.

Further, it is well known that as sufferers from this headache begin to grow old, their attacks may become both less frequent and severe, or may entirely cease. Now such people, I am inclined to think, have some relative weakness of the heart, so that the tension necessary to produce migraine can no longer be maintained.

I shall probably be reminded by pathologists that the wall of

the left ventricle grows thicker with advancing age ; this shows, no doubt, that the heart has more to do at 65 than at 35, but not that it does it better at the former age than at the latter.

A case in which I was much interested a few years ago furnished, I think, what was probably an instance of this. After years of periodical suffering in extreme old age, with marked signs of debility, the headache disappeared, but was replaced by more or less periodical attacks of palpitation, that is to say, whenever there was uricacidæmia and the arterioles contracted, the heart failed and palpitated and could not keep up the pressure (see p. 109). In this case there was no doubt about an excessive excretion of uric acid, as the patient was greatly troubled with uric acid gravel.

When, on the other hand, a migraine, which has been habitual for many years of life—once in a month or oftener—suddenly becomes more frequent and severe, make quite sure that you have not to deal with the onset of nephritis ; I have several times been misled in this way till I examined the urine. Nephritis (as we shall see in chapter xiii.), generally means chronic uricacidæmia, hence the uric acid headache will become more frequent and severe contemporaneously with its onset, will be more difficult to treat, and less amenable to drugs and diet. As will also appear in chapter xiii., I regard uricacidæmia as a contributing cause of the nephritis, though where this complication has supervened it will make the blood condition still worse.

If there is no sign of Bright's disease look for morbus cordis, which may intensify the bad effects of uric acid on the circulation, or failing this, inquire for recent severe illness, new growth or other cause of failing nutrition.

I recently had an illustration of one of these points in the case of a lady who came to me with all the signs of chronic uricacidæmia. I could find no morbus cordis though she had the cardiac signs of uricacidæmia ; I therefore suspected the kidneys, but there was no albumen. I had to confess that I could not account for the symptoms, but a few months later it became evident that she was suffering from cancer of the œsophagus, and this had no doubt been the cause of her low nutrition and uricacidæmia.

I mention this here because it is necessary to bear in mind

that the uric acid headache associated only with functional disturbance is a very different matter, both as to prognosis and treatment, from that which is associated with organic disease.

The functional trouble is rather a warning or danger signal —a sign of temporary high arterial tension—than a sign of actual disease, and with a little attention to diet it may be permanently and completely relieved.

The migraine associated with organic disease is always more serious, it may be a later stage of the functional trouble, or the organic disease (nephritis, morbus cordis, arterial degeneration, &c.), may be a co-result of more or less chronic and unrelieved uricacidæmia; but whatever its exact origin, the treatment is now that of the organic disease, and if we succeed in relieving this the migraine will improve along with it.

In this latter case, however, success is much more difficult to attain, and unless functional and organic cases are clearly distinguished, which cannot be done without great care, the treatment I suggest may get less credit than is due to it.

Diagnosis.—When there is a paroxysmal headache lasting from six to thirty-six hours, which has recurred every seven to ten or thirty days for many years, which is accompanied by a slow high tension pulse, and a scanty excretion of urine, with marked coldness of the skin and extremities, which in a female very frequently occurs in relation to the menstrual epoch, or in a male is apt to follow the day after some unaccustomed muscular exertion, or sexual intercourse, there can hardly be much doubt about the diagnosis.

Organic headaches sometimes resemble migraine; but the paroxysmal history is absent, and when a headache has lasted more than thirty-six, and certainly when more than forty-eight hours, migraine should be considered very doubtful.

The indications for treatment are—(*a*) *during the attack* to clear uric acid out of the blood as quickly as possible by means of any of the drugs which have this effect. One of the best ways is to take calomel, finely divided, with sugar of milk, say gr. $\frac{1}{5}$ every half hour for three or four doses. If there is nausea or vomiting put a mustard leaf on the epigastrium for twenty to thirty minutes before using drugs by mouth. A small injection of morphine may relieve the head where there is deficient gastric absorption, or temporary relief may be obtained by compressing

the carotid. (*b*) *Between attacks*, to diminish the amount of uric acid introduced in food by avoiding animal foods, soups, and extracts which are rich in it (see chapter xvii.), also strong coffee, tea, and vegetable alkaloids, and to clear out any accumulations of uric acid already existing in the body, this may be accomplished by a course, or several courses, of salicylates at intervals. To reduce if need be, the formation of uric acid by reducing the whole nitrogenous metabolism, so far as this can be done without injury to health and strength. Probably a man who is free from organic disease, and excretes on ordinary diet upwards of $3\frac{1}{2}$ grs. of urea per pound of body weight, may safely reduce his income of animal nitrogen so as to bring his urea down to $2\frac{3}{4}$ or 3 grs. per pound.

In many cases, as in my own, change of diet is all that is necessary, and I get numerous reports of cases where this has been so. Dr. Logan, of Ecclefechan, N.B., kindly mentions several. In some there were "bilious attacks, with headache, sickness, rigors, and diarrhœa" and others with headache and sickness of many years' standing, all practically cured by diet; and of one of these he says that when out at dinner or a dance "if she takes a meat dish to save being remarkable she always suffers headache and depression within two days," the exact parallel of my own experiences. (Similar cases are also recorded by Dr. Eskridge and Dr. Ferguson. See references in chapter vii.).

CHAPTER VII.

Epilepsy, Convulsions, and Hysteria.

What I have just said as to the probable mode of production of the uric acid headache applies almost word for word to the causation of its near relative, epilepsy.

Thus du Bois Reymond, whose vaso-motor explanation of migraine has been quoted, goes on to speak of epilepsy as follows: "Singularly enough, if Kussmaul and Tenner's doctrine is right, which places the origin of many epileptic seizures in a spasmodic constriction of all the arteries of the head, then my migraine would be distinguished from this kind of epilepsy less by the nature of the disturbance which prevails in it, than by its degree and extent" (quoted by Liveing, "Megrim and Sick Headache," p. 300). And Dr. Liveing himself remarks, in speaking of epilepsy (p. 205), "This is doubtless the particular neurosis which exhibits the closest connection with megrim both in the occasional replacement of the one affection by the other, and also in the occurrence of cases of a character intermediate between the two."

It was my meeting with these views and quotations in Dr. Liveing's work that set me to look for a uric acid fluctuation in epilepsy similar to that I had already found in headache, and my results in one of the first cases I was able to investigate with sufficient care were published in the *Neurologisches Centralblatt*, March, 1888, and they showed that in seven hours preceding the fits the uric acid excretion was very small, having a relation to urea of only 1 to 50, in spite of the fact that these hours included the alkaline tide after breakfast (see previous remarks on artificial production of headache, p. 118), when the excretion of uric acid should normally have been large;

and just as in the case of the uric acid headache, the uric acid thus held back in what should have been the alkaline tide found its way into the blood later in the day, and produced the fits; the uric acid excretion rose with each set of fits and fell in the interval between them, and with the most severe fits which occurred in the early morning hours of the following day the uric acid rose very high above urea, having the relation to it 1 to 20, and when the fits finally ceased it returned nearly to normal (level of formation) 1 to 33.

Here, then, we see a series of epileptic fits corresponding to a headache, like it, preceded by a minus excretion of uric acid, which in both cases is accompanied by feelings of happiness, well-being, and mental brilliancy (due to absence of uric acid from the blood); like it also accompanied by an excessive excretion of uric acid, which is to a considerable extent proportioned to the severity of the fits, and like it also, in that when the fits cease the excretion of uric acid falls quietly to the level of formation; the plus excretion during the fits exactly balancing the minus excretion that preceded them, as pointed out in the paper just referred to, and in the case of headache the same fact is mentioned in the *Medico-Chirurgical Transactions*, vol. lxx., and elsewhere.

Will it be considered that I was very rash in concluding, as I did from these facts, that the fits were due to the uric acid fluctuation? I confess that if I had had no previous experience of the uric acid headache, if I had not known that I could produce it or remove it at pleasure by influencing uric acid, I might have drawn a different and, I believe, less correct conclusion as to the causation of some of the fits of epilepsy. I have elsewhere quoted from Dr. Ross ("Diseases of the Nervous System," ed. i., vol. ii., p. 916), notes of a case which show that epileptic fits may be preceded by just the same feelings of happiness, well-being, and mental brilliancy that have been observed in the case of headache—symptoms which in both diseases are due to the same cause, and in both are contemporaneous with a minus excretion of uric acid in the urine.

Epilepsy resembles uric acid headache in the mental brightness and well-being, with scanty excretion of uric acid, which may precede both, in the excessive excretion of uric acid and

mental depression which accompany both, and in the subnormal surface temperature (also due to uric acid) which may be found with both, and in both the pulse may be slow and faltering, as it often is when the tension is high. (See also M. Ch. Féré, *Progres Medical*, vol. i., 1889.) Both come on early in life and last for years, both are periodical, recurring at more or less regular intervals—a character common to other functional disturbances produced by uric acid. Both are often met with in members of the same family, or may affect alternately one and the same patient.

Among drugs the action of acids, nitrites, opium, iron, and quinine is almost exactly parallel in the two disorders.

Both again bear identical relations to dyspepsia, ingestion of indigestible food, or other excess, to menstruation and other causes of functional disturbance which produce uricacidæmia.

It seems to me that the parallel between the two neuroses previously noted by Liveing and others, could hardly be more complete; my researches also bring out the nature of the relationship of these functional disturbances to gout which had so often been suspected by previous observers.

Since I discovered that, as the observations of the above quoted authors had led me to expect, there was a fluctuation in the excretion of uric acid with the fits of epilepsy just as with the attack of migraine, I have investigated with interest all cases of epilepsy that have come in my way, and though I have estimated, or been able to estimate the uric acid excretion in only a few of these, I believe that in the great majority I have found more or less well-marked signs of a uric acid fluctuation corresponding with the attacks, such as profuse urine before or after the fits, or both, scanty urine at the time of the fits, evidence of slow high tension pulse with mental depression or dulness before the fits; then again, their relation to menstruation, fatigue, dyspepsia, &c., is often obviously the same as in the case of the uric acid headache. Several of the cases I examined had only slight fits with momentary unconsciousness, and the urine of these never showed any uric acid fluctuation, probably because the plus excretion lasted only a very short time, and the amount of urine already in the bladder completely overshadowed it.

On one occasion, however, a case which had previously with

slight fits yielded only negative results, had a very severe fit with insensibility lasting for twenty minutes. At the end of the insensibility I was able to obtain some urine, and this was placed in a glass near me while I was seeing my other patients. I noticed that it soon became cloudy, with a pale sediment which I regarded at first as mucus, but on closer inspection I found that the pale sediment was rapidly falling through the fluid and collecting at the bottom of the glass.

When my work was over, the urine being even then scarcely cold, I put some of this sediment under the microscope and found that it consisted of colourless lozenges of uric acid; and on estimating the specimen I found that it contained a very great excess of uric acid, its relation to urea being 1—17. Here a case which gave no visible reaction with slight fits, gave a very marked reaction when a more severe fit occurred, so that in this case also the excess of uric acid was proportional to the severity of the fits.

It will easily be understood that when the fits give no warning of their approach, it is no easy matter to separate the urine excreted during the fit, it is almost impossible to prevent there being an admixture of before and during, or after and during, which, as will be remembered in the case of headache, gave me for a long time only negative results; but once the importance of attending to this point is understood, it is easy in the case of headache to separate the urine corresponding to the headache; but in epilepsy it is always difficult, sometimes impossible. In the epilepsy case narrated in the *Neurologisches Centralblatt* the urine was drawn at the end of each fit, and in some cases at the beginning of the fit also, but even then there was some admixture of the excretion of the fits with that of the intervals.

A case will illustrate what I mean. B. B., female, aged 20. Fits began at 12 years old. Longest time without any fits, one month; has had seven or eight in twenty-four hours; they are generally at night or early morning now. Are worst at catamenial period; but has them also between the periods. Father no gout or rheumatism; used to have "bilious headache." Mother suffers from headache, &c. Maternal aunt the same. Has one brother and one sister both subject to headaches; the sister has them about once a week, no fits.

Patient does not know when fits are coming.

Bites her tongue in the fits.

Had scarlet fever at 11 years of age.

Measles and whooping-cough as a child.

Had bad fits three days ago. Catamenia present now.

There is a recent scar on right side of tongue.

Fifteen days later had a fit at 2 a.m.

Urine was saved in two lots—(1) that passed at midnight before the fit, (2) passed a quarter of an hour after the fit at 2.15 a.m. No. 1 was 188 cc. and showed a relative excretion of uric acid 1 to 34, and No. 2 was 97 cc. and gave a relation 1 to 41. There was, therefore, relatively less uric acid in the period, two and a quarter hours, in which the fit took place ; but it will be seen that the separation was anything but satisfactory, and No. 2 was obviously made up of the minus excretion before the fit, as well as the plus during, and the minus far outweighed in time and quantity the plus.

It is clear that even a few positive results must far outweigh such negative results as this, even if one had not the exactly parallel case of headache to argue from. (See page 3.) I have sometimes got patients to pass water every hour of the waking day, then when a fit occurred there was never very much water in the bladder, and in some cases there might be almost none at the beginning of a fit, and so the urine excreted from the kidney during the fit would be obtained pretty pure.

Drs. C. A. Herter and E. E. Smith, who have made some interesting researches on the relation of epilepsy to the excretion of uric acid, with a view of testing my results[1] have not, it seems to me, paid sufficient attention to this question of separation.

The smallest amount of urine examined in their tables is 134 cc., and this was not at the time of an attack of grand mal. All the amounts estimated at the time of an attack of grand mal were larger than this.

Now the amount of urine excreted in an ordinary grand mal attack, lasting, including the stupor following the fit, 20 to 30 minutes, could not be much more than 30 cc. ; therefore, even under the most favourable circumstances, the urine of an attack was mixed with two volumes of urine excreted before or after it, and no excess of uric acid would, therefore, be expected.

[1] See *New York Medical Journal*, August, 1892.

As I have pointed out, even in the case of the uric acid headache, the excretion of the whole day may show minus uric acid, while if the urine of the attack is carefully separated, it shows plus uric acid corresponding to the hours of headache. (See *Journal of Physiology*, vol. xiii.) In my case of epilepsy, published in the *Neurologisches Centralblatt*, to which these authors refer, the urine of each fit was separated as carefully as possible; and I also pointed out that when the urine of the fits was mixed with that before and after them, the uric acid came out normal, while the urine secreted during the fits showed a great excess.

I certainly think it is quite useless to examine 150 to 500 cc. of urine, when that excreted during the fit could not possibly exceed 20 or 30 cc.

The authors say again, on p. 234: "The latter [that is, urines passed immediately after seizures] are apt to show a higher uric acid ratio than the urines passed just before seizures; very often, however, the ratio is one that belongs within the limits of health."

This is just my result diluted, and as the quantities are not given there is nothing to show that the urine just before was not the urine of two to three hours before, *i.e.*, a mixture; or that the urine passed after the fit really corresponded only to the excretion of the fit.

Further down on the same page they say: "The excess of uric acid that is observed in epilepsy cannot reasonably be construed as the cause of the seizures." They acknowledge, then, that there is an excess, but differ from me as to the relation of cause and effect.

In petit mal, however, they found a distinct relation between the excretion of uric acid and the cause of the seizures, and treatment by milk diet greatly reduced the frequency of the attacks. (Prev. ref. p. 239.)

This is just what I should expect, as in my writings on the subject I have not limited myself to grand mal, but have suggested that petit mal, hystero-epilepsy, and hysteria are all similarly related to uric acid.

Where attacks of petit mal are frequent I should expect a continuous plus excretion of urates; but, as I have often proved, it is useless to look for a urate reaction in a single short

attack, as the separation of urine can never be sufficiently good.

If Herter and Smith will separate the urine of grand mal cases with greater precision, I have no doubt that they will get urate reactions similar to mine, and if they will also treat grand mal to the same diet as petit mal they will, no doubt, get some satisfactory results, just as others have already done.

The observations of these authors on the relationship of the fits to intestinal putrefaction are of extreme interest because they supply a further illustration of a point which I had previously noticed. Thus, in *St. Bartholomew's Hospital Reports*, vol. xxiv., p. 226, I have made the following remark: "Salicylates again may fail to be absorbed for a time from gastric irritation or other causes, and I had a remarkable instance of this in a case of epilepsy which I was treating with this drug. On several occasions the urine gave no reaction with perchloride of iron during the fits, though on some occasions there was probably as much as 20 grs. of the salicylate lying in the stomach, and there was a strong reaction in the urine after the fits had passed off, without any more of the drug being given."

I notice also with interest that M. Ch. Féré records (*Progres Medical*, December, 1888, p. 452) that there is a lowering of tension in the renal vessels at the end of the epileptic paroxysm, accompanied by increased elimination of drugs, and this practically demonstrates that there was high tension and diminished elimination of drugs during the paroxysm.

I can now explain all the facts much more completely than I could at the time the above was written, for I now know that when uric acid in the blood raises arterial tension it contracts the arterioles and capillaries throughout the whole body; so that not only are the urine and saliva scanty, not only is the skin cold and dry, but all the gastro-intestinal secretions (gastric juice, bile, pancreatic and intestinal juices), are similarly diminished, and the circulation through their mucous membranes is so imperfect that digestion and absorption come to a standstill. This and the generally diminished metabolism accounts for the marked fall in urea excretion that generally accompanies a plus excretion of uric acid, and the resumption of these physiological

processes accounts for the rise of urea when the urates are cleared out of the blood, and their excretion in the urine diminished.

But such a marked arrest of gastro-intestinal digestion will almost certainly be accompanied by the onset of putrefactive processes — the processes of which Herter and Smith have observed some of the results.

All is now clear; the reason the salicylate failed to appear in the urine in the above case was because the arterioles were contracted, and gastro-intestinal digestion and absorption were at a standstill.

We can now see clearly the origin of the horrible fœtid dejecta often met with after an attack of dyspepsia, bilious attack, or uric acid storm; also why calomel so promptly puts matters of this kind right. I used to think that it acted directly as an antiseptic, but it is now evident that its most important action is the result of its chemical relations to uric acid, by which it clears urates out of the blood, relaxes the arterioles and capillaries, and allows gastro-intestinal digestion to proceed once more. (See p. 35.)

The intestinal putrefaction noticed by Herter and Smith, far from being the cause of the fits, is but a result of uricacidæmia. The contraction of arterioles which produces the high tension, which in turn interferes, as I have pointed out above, with the intra-cranial circulation and produces the fits, interferes also with gastro-intestinal digestion and allows putrefaction to take its place.

Like the uric acid headache, uric acid epilepsy is often strictly periodical. M. H., the case whose excretion in a series of fits is given in the *Neurologisches Centralblatt*, has been under my care ever since, and my notes show that in her case the fits come with considerable regularity every fourth week; occasionally there is a slighter attack at a two-week interval. Again, in this case the fits almost always come at a time when the excretion of uric acid is naturally large—as in the early morning, when the acid tide of the night has run itself out, and with falling acidity there is a plus excretion of uric acid. Then on occasions too numerous to mention, the fits in this case have been obviously precipitated by causes which would produce a uric acid fluctuation and its temporary excess in the blood.

Thus one morning in the early alkaline tide she was standing

on a chair when a fit caused her to have a bad fall and cut open her chin. Chloroform was administered, and the wound was sewn up, but the chloroform upset her stomach and produced vomiting, and she had a series of extremely severe fits. Obviously the vomiting would diminish acidity and flood the blood with uric acid.

Again, this patient has often told me that though she had no warning of the individual fits, she generally feels more heavy and drowsy on waking on those mornings on which she subsequently has fits, and this is a complete parallel of the uric acid headache, the heaviness and drowsiness and disinclination for getting out of bed, being in both cases the work of uric acid, and to my mind a proof of its excess in the blood. Of the heaviness and stupor that follow the fits I have spoken elsewhere (*Brain*, Spring Number, 1891, p. 83), and have pointed out that this also corresponds with the work of uric acid, but (as pointed out by others) is not proportional to the severity of the fits.

While speaking of this case I will just mention a few points in treatment which it appears to illustrate.

One of the first things I did after getting a uric acid reaction in this case was to put her on salicylate of soda, and for a long time she appeared to be doing very well on it, and she said that she was brighter and better in herself—a remark which is made by many epileptics when put on this drug.

The fits, however, returned, and it is doubtful whether the apparent improvement under salicylates was more than one of the natural fluctuations in the frequency of the attacks, as this drug was tried to a much larger extent by my friend Dr. Tooth, at the National Hospital, Queen Square, and though most cases were brighter and better at first they afterwards relapsed.

But salicylate of soda is undoubtedly a double-edged weapon; it promotes the excretion of uric acid, it is true, but in a disease like epilepsy this is often a cause of danger, for if the drug is taken irregularly its action may fail and leave a considerable amount of uric acid (so to speak) stranded in the blood, and if some of this gets into combination with an alkali it will produce a fit, and a headache as I know can be produced in the same way. Again, salicylate will sometimes upset the stomach when taken irregularly or at the wrong hours, and the gastric upset will not only prevent the action of the salicylate, but will bring about a rise in alkalinity and precipitate a uric acid storm.

My impression is, therefore, that in epilepsy even more than in headache diet is the only thing that holds out much hope of controlling the uric acid. In the following case it appears that diet coupled with somewhat severe purgation did put a stop to the fits, and I have previously mentioned (p. 113) a similar case from the experience of the late Dr. King Chambers, while recently I have heard from quite a number of colleagues and others, that they have put my suggestions in practice with more or less benefit to their epileptic patients; though much more experience is required before we can safely build on the results obtained, except as indications and encouragement to try the same treatment in what appear to be similar cases.

I owe the notes of this case to the kindness of a patient who, having relations in the profession, was able to appreciate the bearing of his relative's case upon my researches: it is that of a gentleman, aged 50, who had suffered from fits all his life, and was cured by a severely vegetarian diet, with a purgative dose of calomel and colocynth, followed by Haust. Sennæ co. twice a week, he lived twenty years more without any fits at all.

He lost weight very decidedly, and was considerably weakened by the treatment, and I think it probable that the urate formation was not only greatly reduced, but that the heart was also much weakened by the severe treatment, and hence was incapable of keeping up so much tension as was necessary to compress the intra-cranial veins.

Probably this treatment was unnecessarily severe; at the same time there are, no doubt, plenty of epileptics who would be glad to purchase freedom from their disease at even greater cost.

The treatment in the above case was recommended by a Dr. Pelham Warren, long since dead, and the directions say, among other things, "the medicine is meant to remedy the mischief arising from an inactive state of the liver, indigestion, &c., but the constitution cannot be freed from the unhappy tendency to pressure on the brain and convulsions without the strictest persevering attention to diet."

"Pressure on the brain" is an extremely good and possibly accurate description of the real condition present, and it reminds us of what patients with headache or depression so often say—that their head is bursting, or their brains boiling over. We can

now realise much more thoroughly the condition of affairs that underlies these sensations.

Among others I have heard from Dr. Logan, of Ecclefechan, N.B., of a case of epilepsy of twenty years' standing, which has apparently benefited very greatly by the diet treatment I suggested after bromides had failed and been left off; and quite a number of cases similarly improved on a diet of vegetables and milk are quoted by Dr. J. Ferguson, of Toronto, in a paper, "Some Remarks on Epilepsy," read before the Huron Medical Association, and in a later paper (*Alienist and Neurologist*, April, 1893). Dr. J. T. Eskridge, of Denver, Colorado, has written on these subjects in the *Alienist and Neurologist* for January, 1892, and I have since heard from him that he is getting many excellent results, and I cannot but regard these reports as very hopeful.

As I have previously pointed out, Sir W. H. Broadbent, in his very interesting book on "The Pulse," p. 120, says, in reference to Tripier's theories about the pulse of epilepsy: "I think it is the slowing of the circulation which causes the convulsions," and a little further on he says, "I look upon convulsive attacks, when they occur in connection with an infrequent pulse, as a result of cerebral anæmia, produced exactly in the same way as the convulsions after great hæmorrhage;" and again he says, "The late Dr. Moxon, it will be remembered, went so far as to suggest that the initial event in common epilepsy was a stoppage of the heart." See also an interesting paper, "Experimental unter-suchungen über anæmie und Hyperæmie des Gehirns in ihren Beziehung zur Epilepsie" (*Archiv. de Physiologie*, June, 1891, p. 609).

Now it seems to me we have in the effects of uric acid on the circulation—about which I have said so much—a direct cause of just such alterations in the cerebral circulation as Sir W. H. Broadbent here refers to. For my part I should be inclined to state the case for the causation of fits by uric acid somewhat as follows: In 1888 I pointed out that some epileptic fits are accompanied by a characteristic fluctuation in the excretion of uric acid, in that there is a minus excretion of that substance before and after the fits, and a corresponding plus excretion during their continuance, and this observation has since been repeated by myself and others; and, as has been pointed out, very many of the signs and symptoms of epileptic and other fits are the signs of uric-acidæmia.

Further, it is very improbable that the fits are the cause of the large excretion of uric acid, because this is but the natural result of a fluctuation in excretion which took place hours before the fits began. On the other hand, it is extremely probable that uric acid is the cause of the fits, because I can practically prove that it may produce such changes in the circulation (stasis, &c., as Sir W. H. Broadbent and others believe to be the cause of fits. (See p. 123, and *Brain*, spring and summer number, 1893.) Exactly the same argument applies to the causation of puerperal and uræmic convulsions. Pregnancy is undoubtedly a time of greatly increased metabolism, during which there is sure to be considerable storage of uric acid which finds its way into the blood as soon as digestion and metabolism are upset by the pains, troubles, and fatigues of delivery. In Bright's disease again there is nearly always high arterial tension and excess of uric acid in the blood which produces it, and it needs but a slight fluctuation in excretion to produce stasis and hyperæmia in the intra-cranial circulation and possibly œdema of membranes as well.

I believe that hysteria and hysterical fits bear the same relation to uric acid as the fits we have been speaking of, and that many of the minor symptoms of hysteria are the signs of uricacidæmia.

I have pointed out in relation to the effects of uric acid on metabolism (chapter iv.) that the passage of a large quantity of uric acid through the blood is generally accompanied by a fall in the excretion of urea (*i.e.*, probably in the formation of urea) while, on the other hand, the clearing of uric acid out of the blood by anything that quickly produces this effect is followed by a rise of urea; these urea fluctuations probably affording to some extent a measure of the effects of uric acid on metabolism, and have suggested that the rise of urea noticed by MM. Gilles de la Tourette and Cathlineau (*Progres Medical*, vol. i., 1889) as occurring at the end of an attack of hysteria is due to the same causes; they notice that the urea is diminished in the twenty-four hours including the attack, and when the attack is coming to an end as the arterioles begin to relax, there is a rise of urea from increased metabolism; no doubt also the circulatory troubles which interfere with metabolism in the muscles, liver, &c., will interfere with or temporarily suspend gastric digestion also. The above authors

also mention that there is a marked temporary polyuria affecting the first micturition after the attack, and remark that the cause of this polyuria is not completely known: but if the attack is attended, as I believe, by high tension and contracted arterioles, and if as it passes off the arterioles are relaxed there is not much difficulty in accordance with my previous arguments in completely explaining the temporary diuresis. (See p. 93). Probably the correct way to state the case would be to say that the relaxation of arterioles which allows a free circulation in the kidney and a diuresis allows also a free circulation in the brain, and the mental faculties regain their normal equilibrium; it is, in a word, the circulation which acts on the nerve centres just as it acts on the skin, muscles, liver and kidneys and perturbs their functions.

I have found excess of uric acid in the urine in some hysterical attacks, and I look upon the nervous symptoms as the results of the circulatory disturbances produced by uric-acidæmia; and this same cause will account for the fall of urea during and the rise after as well as the diuresis which follows the attack, which these authors acknowledge that they are unable to explain.

It seems, then, that epilepsy is not only, as has long been known, related to gout and to migraine, but it has, as I have pointed out, an important relation to the relative excretion of uric acid in the urine, an excess of uric acid in the urine being the index of an excess in the blood, and this by its effects on the vessels may be the actual cause of such changes in the cerebral circulation as will give rise to fits.

Thus my observations and reasoning, founded on clinical relationship, appear to afford us a fairly good working explanation of the causation of these diseases.

What I said about the association of the uric acid headache with nephritis, applies also to epilepsy in any case that is due to uric acid, for nephritis means chronic uricacidæmia, and with this the fits will be more frequent and severe and less amenable to drugs and diet, than in cases where the kidneys remain sound. Do we not get here also a side-light on the causation of the headache and fits of uræmia? As I have pointed out, the treatment of uricacidæmia removes the symptoms of uræmia (*Brit. Med. Jour.*, November 30, 1889). See also chapter xiii.

Diagnosis.—The time has not yet arrived for any dogmatic statements on this point; but where epileptic fits have recurred with more or less regular periodicity for a long time, and also resemble migraine in their relation to dyspepsia, muscular exertion, or menstruation, are accompanied by scanty urine, and preceded by a slow or faltering pulse, and when also there is no organic cause to be found to explain their occurrence, I would suggest that they may be due to the effects of uric acid on the circulation in the skull, and that further investigation or treatment from that point of view is indicated.

The Indications for Treatment are very much the same as in the case of migraine. An attempt may be made to break through the fits or the stupor and headache which follow them by the use of such drugs as acids, calomel, morphine or the nitrites with or without temporary compression of the carotid.[1]

As regards uric acid the indications are to reduce the amount stored in the body, and the amount directly introduced into the body, and it may be necessary to go further, and greatly reduce metabolism and nutrition so as to weaken the heart and muscles and thus permanently lower arterial tension. (See case previously mentioned.)

[1] For cases where this was done, see *Lancet*, vol. i. 1892, 358, and vol. ii., 1892, 662.

CHAPTER VIII.

Mental Depression and Fatigue.

Mental depression is a concomitant symptom of the uric acid headache, and I soon found that by influencing the uric acid I could produce or remove it along with the other symptoms. (*Practitioner*, November, 1888, paper on "Mental Depression and the Excretion of Uric Acid.")

The condition which accompanies the uric acid headache, forming a sort of halo round it, is one of dulness and inability for effort, either mental or bodily, with forgetfulness of names, persons and things. It is closely related on the one hand to sleepiness, and on the other to a mental disposition to take the worst possible view of self and all that concerns it. In this condition self-reliance is absolutely gone, extreme modesty is common or even habitual, a feather weight will crush one to the dust, and even the greatest good fortune will fail to cheer.

If roused from such a condition a considerable amount of irritability and bad temper is sure to be manifested quite out of proportion to the requirements of the case, so that those around a sufferer are soon able to diagnose the condition for themselves.

It seems to me that mental depression is occasioned by a slighter grade of the same condition that produces the uric acid headache, that is to say, a less intense uricacidæmia; while I now rarely or never have enough uric acid to produce a bad headache, I pretty frequently have enough to produce some irritability and mental depression, though this also is slight compared to what it used to be.

On the other hand, clear the blood of uric acid by the use of any of the drugs which produce retention of it, and as the pulse tension is reduced, its rate quickened, and the urine increased, the mental condition alters as if by magic, ideas flash through the brain, everything is remembered, nothing is forgotten, exercise of mind and body is a pleasure, the struggle for existence a glory, nothing is too good to happen, the impossible is within reach, and misfortunes slide like water off a duck's back (well-being). To such a terrible extent are we the creatures of the circulation in our brain.

Some have asserted that it is oblivion men seek for when they take opium, cocaine, &c. I believe this to be a great error. Give me an eternity of oblivion, and I would exchange it for one hour with my cerebral circulation quite free from uric acid, and opium or cocaine will free it for me, but as I shall show later on there are other and better ways of obtaining this freedom.

A few years ago (1890) *Punch* gave an extremely interesting illustration of the condition I am here speaking of. I did not note it at the time, and cannot now give the reference, but it was somewhat as follows:—A young or middle-aged man is represented reclining in an easy chair in a comfortable or even luxurious sitting room. I think, but I am not quite certain, that the hour is said to be afternoon. On the floor near him is lying a dog resting or sleeping with half an eye open. *Punch* then goes on to tell that this young man, in spite of his comforts and luxuries, is not happy, and the cause of his misery is the uncomfortable thought which has gradually forced itself into his brain that his dog does not love him. Presently he rouses himself sufficiently to call his dog with the object of putting to a test the cause of his misery, but the animal rushes towards him and evinces such evident signs of pleasure and affection that his master is soon compelled to abandon the idea that his dog does not love him. The young man who is thus unable to make himself believe that his dog does not love him is still unhappy, and he rushes in search of a subject to the opposite pole and begins now to worry himself because he does not love his dog. This is more difficult to disprove, and probably the idea lasts him for the rest of the afternoon, but *Punch* intrudes no further upon him.

Now, I have no doubt whatever that this is drawn from

nature, for I have seen many similar cases, and it well illustrates what I want to point out, namely, that the cause of misery is central (the circulation in the brain), but the mind seizes first on one subject and then on another, about which to worry itself. This young man, in exceptionally fortunate circumstances, could find nothing more serious than the mutual affections of himself and his dog, but no doubt he extracted as much misery from these as another man with a similar condition of brain circulation would do from what might appear to others to be more serious troubles. The fact that the cause is central, not external, is abundantly proved by the mind wandering to cause after cause as the ones on which it first pitches are shown to be shadows.

"Is life worth living?" That depends on uric acid. The orthodox answer is "that depends on the liver," but as the liver is only one of the sources of uric acid I cannot regard the answer as sufficient.

Soon after I wrote my first paper on mental depression (*Practitioner*, previous reference), Professor Lange, of Copenhagen, kindly wrote to me and sent me a monograph which he published in 1886 on periodical depression and its connection with the uric acid diathesis (*Om Periodiske Depressionstilstande, Cobenhavn*, 1886).

His clinical observations and his treatment of the trouble ran parallel to my own, but he knew at that time nothing about the relation of the disturbance of function to uricacidæmia, and merely treated in a general sort of way the uric acid diathesis, which he had found by clinical observation to be related to this periodical depression.

His observations and clinical experience are of great interest as confirming my own, but he had got but a small way into the real pathology of the trouble.

Not long after this, in a review of some of my researches on uric acid, Dr. G. Hofmann (*Prager Med. Woch.*, 1889, No. 28) mentioned, in reference to my assertion that acids cleared the blood of uric acid and produced a condition of mental brilliancy and well-being, that there is a proverb current in some parts of his country as follows: "Es est ganz. merkwurdig dass in Westböhmen, vielleicht auch anderswo das volk den sauren speisen einen gunstigen Einfluss auf die Gemuthsstimmung zuschreibt; wenigstens ist dort das sprichwort, sauer macht

lustig gang und gäbe." This is exactly my experience, and acids do it by affecting uric acid; when they fail to affect the uric acid they do not do it.

As before said, arterial tension is directly proportional to the amount of uric acid circulating in the blood, but arterial tension means and is due to contraction of arterioles and capillaries; therefore contraction of arterioles and capillaries is proportional to the amount of uric acid in the blood.

But contraction of the arterioles and capillaries in the brain means, probably, stasis and hyperæmia of the brain. Therefore, *cæteris paribus*, stasis and hyperæmia of the brain are proportional to the uric acid in the blood.

Now, it is well known that in mental activity and excitement the brain is large and its cortex hyperæmic, and under opposite conditions it is relatively small and anæmic. It is also anæmic in sleep.

With regard to this point, Dr. S. G. Burnett, in a lecture on "The Diagnosis of Incipient Melancholia" (*New York Medical Journal*, May, 1891, p. 497) says: "In melancholia there is a dejected and subdued appearance with decreased activity of mind and body, slow defective mental reflexes, and a delirium of self-reproach and persecution. Meynert believes the symptoms found in melancholia are the result of an anæmic condition of the cerebral cortex. Clinically we know that an abnormally anæmic condition of any organ means starvation, followed by a decrease and change in function, and if continued long enough the condition must become degenerative in character." And with regard to these remarks about anæmia and hyperæmia, it seems probable that stasis and hyperæmia effect, in exactly the same way as anæmia does, the interchanges between the blood and the tissues of the brain, hence their effects are similar or identical.

Among the symptoms of incipient melancholia the writer just quoted lays great stress upon pain in the back of the neck (neuchalalgia), insomnia and mental depression when occurring together. From his description of neuchalalgia it seems to be identical with my uric acid headache, which, when very severe, is right in the centre of the occiput, just above the insertion of the ligamentum nuchæ, and about insomnia accompanied by high tension Sir W. H. Broadbent and others have written.

The great point about the mental depression due to uric acid is, as rightly insisted on by Professor Lange, that it is periodical, in which it resembles the uric acid headache and the fits that are due to the same cause. Where depression is chronic and continuous, with but little fluctuation, it is more probably due to morbus cordis or other organic cause, than to uric acid, though, as I said just now, uric acid may intensify the effects of organic disease.

We have then a condition of mental depression, between which and melancholia with delusions I agree with Sir W. H. Broadbent in believing that there is no absolute line of demarcation (see Croonian Lectures, 1887), and this depression is due to a certain amount of stasis and hyperæmia in the brain, brought about by the high arterial tension which an excess of uric acid in the blood (uricacidæmia) produces. If this is the case the depression in question should bear just the same relation to the excretion of uric acid as the other diseases of which I have spoken, and a great many factors that influence uric acid should alter in one way or another the depression it causes.

In physiological conditions we have seen reason to believe that there is more uric acid in the urine, and more in the blood in the alkaline tides of the day than at night, that the excretion of uric acid is relatively greater in the summer than in the winter, and that consequently there is more in the blood in the former than in the latter.

Therefore, mental depression that is due to uric acid should be worse in the alkaline tides of the day, especially in the morning one, and it should be worse in the spring and summer. (See chapters ii. and iii., "Formation and Excretion.")

In my first paper in the *Practitioner*, I remarked on the fact that in France the suicides in July far outnumber those in any other month, and suggested that the effect of season on the excretion of uric acid, might give us a simple explanation of the fact, and I see that some recent French statistics quoted in the *Lancet*, vol. i., 1893, p. 1,413, show that of all suicides, 31 per cent. occur in spring, 26 per cent. in summer, 21 per cent. in autumn, and 22 per cent. in winter; probably the autumn, the first cold after the plus excretion in the summer, furnishes the lowest urate excretion of the year, just as spring, the first warmth after the retention of the cold season, furnishes the largest urate excretion

of the year. I am also inclined to believe, and am collecting records of cases bearing on the point, that the fatal act is more often committed in those hours of the day when the excretion of uric acid and the contemporaneous uricacidæmia are greatest.

Again, it has appeared to me that the irritability and bad temper of uricacidæmia, due to the stasis and hyperæmia it brings about, may account for a certain number of murders, and they also have been noticed to have a seasonal variation. Thus May has been called the month of suicides and murders (*Lancet*, vol. i., 1890, p. 1,208).

May is generally the first month in which we have any warmth, and with the falling acidity some of the uric acid held back and stored in the winter, begins to be dissolved in the blood, and more or less marked uricacidæmia results.

In a word, I believe that the above-mentioned physiological fluctuation in the excretion of uric acid, and the concomitant uricacidæmia completely account for the observed fluctuations in the incidence of mental depression, suicide and murder.

As regards experimental results, I have said that I can produce or remove this mental depression at any time, just as I can produce or remove the uric acid headache, and the slow high tension pulse which accompanies both.

Alkalies will produce it, provided there is some uric acid in store for them to act upon, and acids, opium, cocaine, mercury, iron, zinc, strychnia, &c., will remove it. I have very little doubt that the use of alcohol, opium and cocaine to remove the uricacidæmia and its cerebral effects, has often led to their abuse, for they cure present depression by driving the uric acid out of the blood into the liver, spleen, joints, &c., where it is stored up, but the next time the acidity falls, generally in the alkaline tide of the following day, out it comes again into the blood, and uricacidæmia worse than before, is produced. From this secondary uricacidæmia of what I have spoken of as the rebound, there is, so far as the indulger in opium or cocaine knows, no escape except by repeating the dose, and so he goes on and on, ever accumulating more and more uric acid, and requiring continually larger and larger doses of the drug to keep it out of the blood, and this is the beginning of chronic morphinism.

In my own personal experience I soon got over this difficulty by removing the uric acid from the body. Supposing that I

suffer from mental depression I can remove it by a dose of morphine, say gr. $\frac{1}{6}$, and then I follow this by several xv. gr. doses of salicylate of soda, which, as we have seen, eliminates uric acid best when the acidity is high, and further prevents it from affecting the arterioles to any great extent as it passes through the blood.

The uric acid, held back by the morphine, is thus eliminated by the salicylate; there is, therefore, no uricacidæmia next morning, and no necessity to take another dose of morphine.

This experience has led me to suggest the use of salicylates in the attempt to break through the morphine habit. (See p. 33.)

As regards alcohol, I was much interested to hear it said at a dinner given by the Vegetarian Society of London a few years ago that the adoption of a vegetarian diet was one of the best means of overcoming the craving for drink, for if this craving is in any way due to the mental conditions of discomfort produced by the circulatory disturbances of uric acid, this is just what I should expect.

As regards the production of well-being, the acids mixed with the alcohol are probably more efficient than the spirit itself, but the alcohol, in so far as it acts as a stimulant, would probably raise the acidity, relax the arterioles, and produce some well-being (see p. 109); on the other hand, we know that whiskey has comparatively little gout producing powers — hence the freedom of the Scotch—while acid beer and wines are much more powerful gout producers, though containing less alcohol; and the beverages that produce gout will be the most powerful preventives of uricacidæmia, though any or all of them will relieve for a time mental depression and similar feelings.

In pathology the conditions which produce mental depression are just those which bring about uricacidæmia, such as loss of employment and deficient food, functional or organic disease interfering with digestion and nutrition; anything that diminishes nitrogenous metabolism and the excretion of urea, as the acidity falls with the urea. A man while in good work eats freely of meat and drinks 4d. ale; as a result his acidity rules high, hence he excretes uric acid in the relation to urea of 1—38 or 1—40; that is, the excretion of uric acid falls short of formation, and he daily stores or retains a certain quantity in his body. Now come bad times—he is out of work, can afford no beer, and only

little meat; down goes urea and acidity, and the uric acid he has previously retained at once begins to pass into the blood and urine; there is uricacidæmia with slow high tension pulse and mental depression, and his wife tells you he is fretting because he has no work; but clear the uric acid out of his blood and he will cease to fret though he still has no work.

Then again most fevers, especially short sharp fevers, such as influenza, pneumonia, scarlet fever, erysipelas, produce the material for more or less intense uricacidæmia.

It is well known that fevers raise the acidity of the urine. A very good instance is quoted by Sir W. Roberts of a patient with alkaline urine who contracted erysipelas; the urine became acid during the fever, but the alkalinity returned again as the fever subsided ("Urinary and Renal Diseases," p. 59). And Pieper has shown that all fevers diminish the alkalinity of the blood except such as are complicated by dyspnœa and cyanosis. I have suggested (see p. 61) that in fevers there is increased oxidation which produces both increased formation of heat and increased formation of acids, but where there is dyspnœa or cyanosis oxygen is deficient, and then neither does the temperature rise so high nor the acidity increase so much as in fevers not thus complicated.

But be this as it may fever generally entails a rise of acidity, and this produces a deficient excretion of uric acid and accumulates a store of it in the body; when the fever comes to an end acidity falls and then the uric acid is dissolved out and uricacidæmia results.

Such uricacidæmia will be proportional to the amount of uric acid that was retained by the fever, and it may be reinforced by any uric acid that had been previously stored in the body, hence in the convalescence of acute fevers there is sure to be more or less uricacidæmia, which will continue till the stores of uric acid have been all swept out, or till the acidity again rises with improving nutrition; till one of these things happens there will be daily uricacidæmia with slow high tension pulse and mental depression; this is no doubt the cause of the slow high tension pulse so often seen during the first few days after the crisis of a pneumonia and other fevers—a condition described by Riegel (*Zeits. fur Klin. Med.*, 1890), and others as post febrile bradycardia. (See p. 106.)

I have also mentioned two cases of pneumonia that were under my care about the same time: one was a strong and powerful man, the other a weak and ill-nourished woman; in the former the post febrile conditions, including bradycardia, were very prominent, in the latter very slight, and the difference was simply due to the fact that the big man with his large metabolism of nitrogen stored much urate at the time of the fever, while the ill-nourished woman stored but little, and the post febrile symptoms were proportional in each case to the amount of urate passing through the blood (post febrile uricacidæmia).

Bright's disease again is frequently associated with suicide, and in Bright's disease there is chronic uricacidæmia, with contracted arterioles and slow high tension pulse.

Menstruation should probably have been mentioned under physiology, but in menstruation there is very often uricacidæmia because this condition is commonly accompanied with some disturbance of digestion, failure of nutrition, and fall of acidity. I have already (chapters vi. and vii.) pointed out that women who have fits or the uric acid headache nearly always suffer from attacks at the catamenial period. Sir W. H. Broadbent has remarked that the pulse is often slow and of high tension in menstruation, and Dr. Barnes (*Brit. Med. Journ.*, vol. i., 1890, p. 1,401), has pointed out that museums can easily be stocked with the organs of menstruating women in consequence of the fact that they so often commit suicide at this time.

It seems to me that at this point we are on the borders of a very wide field in psychology which we may presently be able to cultivate to some purpose; and the question presents itself, how far is the bias of women towards religion, and generally to take serious views on matters which men often regard lightly, how far is this due to the more or less continued effects of uric acid on their arterial tension and cerebral circulation? In attempting to answer this question we must bear in mind, as I have said, that depression breeds depression, that once there is an excess of uric acid in the blood this continually tends to depress more and more both metabolism and nutrition and keep them down. In a woman who is strong, active and well nourished, the uricacidæmia of the menstrual period will be quickly put an end to by the rising acidity of an active nutrition; but in one who is weak and ill-nourished acidity may remain depressed for days or

even weeks, she will suffer from chronic uricacidæmia, for the depression of one period will hardly have passed off before the next is due, and its paralysing effects on the activity of mind and body may suffice to give a bias to her whole life; such a woman meets with a disappointment and has not power to throw it off; she mopes and nutrition suffers, and uricacidæmia becomes established with mental depression; she goes in for some morbid religious extravagance, and perhaps ends in a convent. This is an extreme case, but I believe the general bias of the female mind is often determined by similar factors.

In this connection I was much interested to see an article in the *Brit. Med. Journ.*, vol. ii., 1893, p. 258, in which it was said that judging from the advertisements in religious papers the disorders from which their readers most frequently suffered, were "fits and deep depression."

I must now leave my readers to decide for themselves how far the fits and the deep depression, and the morbid religious bias as well, are due to uric acid and its effects on the intracranial circulation; but we all know that there are conditions associated with feeble or failing nutrition and probably uricacidæmia in which "the devil a saint would be."

In several papers also I have mentioned the experiments of Drs. Roy and Sherrington which show that injection of acids into the veins produces enlargement and hyperæmia of the brain (*Journal of Physiology*, vol. xi., p. 85), and have suggested that the acids really affected the vessels and brain circulation indirectly by their action on uric acid.

Roy and Sherrington found on the other hand that alkalies diminished the blood in and reduced the volume of the brain; and here we have, I think, actually demonstrated the effects which I can produce on the circulation of the brain, and so on the mental condition by influencing uric acid.

By giving alkalies I can produce uricacidæmia with slow high tension pulse, contracted arterioles in the skin and kidneys, stasis and hyperæmia of the brain and mental depression; on the other hand by giving acids I can free the blood from uric acid, relax the arterioles, cause free circulation in the brain, and mental brightness and well-being.

If it is objected that the action of the acid in these experiments is too quick for it to have acted indirectly on uric acid I

should reply that in chemistry a precipitate occurs the moment a precipitant is added to a solution, and I fail to see why it should be delayed in the blood in which the action is probably very similar. If it is urged that acids relax and alkalies astringe the capilliaries directly, I should reply that in the human subject if you remove all the available uric acid, alkalies will fail to raise arterial tension, because they fail to produce uricacidæmia. Again, lithia markedly diminishes the acidity of the urine, but yet it quite fails to produce either mental depression or scanty urine, on the contrary it causes well-being and diuresis (see chapters ii. and iii.), and the excretion of uric acid tells us why it does so, for in place of producing uricacidæmia like other alkalies, it clears it out of the blood and diminishes its excretion.

Again lead and iron produce retention of uric acid, and while this action lasts they produce also relaxed arterioles, well-being and diuresis. I have shown that all these substances produce the same effects on uric acid; from the other point of view it would have to be shown that they all separately produced the same effects on the arterioles.

Then again I have pointed out that the headache, slow high tension pulse, depression, and other symptoms of uricacidæmia are proportional in every way to the excess of uric acid in the blood and urine, but bear no relation whatever to the amount of alkali which may have been used to produce them artificially.

In a word all the phenomena are proportional to the uric acid, but not to the drugs which only act indirectly upon it.

And my experience of the effects of diet in my own case (though it by no means stands alone), are amply sufficient to prove this, for if alkalies contract the arterioles of the brain and produce anæmia and depression, headache, &c., I ought to be much worse now on a milk and farinaceous diet, which has greatly diminished the acidity of my urine, but on the contrary I am much better now and have not a tenth part of the headache, high tension pulse, and depression I used to have on an ordinary meat diet, and I am glad to be able to say that many of my patients have now had similar experience. Severe uricacidæmia is now impossible, hence its effects fail to appear, but alkalies are plentiful in the circulation, and have no effect on the arterioles.

And my experience has convinced me that the best way to keep the brain circulation free from uric acid is not to dose it

with opium or cocaine, which, while clearing the blood to-day, store up the poison for future trouble, but to reduce the formation and introduction of uric acid while reducing the whole nitrogenous metabolism, and to provide for its constant free excretion by a plentiful supply of alkali in the shape of fresh fruits and vegetables.

I am here speaking of functional, temporary, periodical depression, though I quite believe that if the vascular conditions that produce it are very often repeated over long periods they may at last bring about some organic changes which are irremediable and cannot be removed. I have, nevertheless, been able to effect great improvement in depression, which had lasted on and off through very many years by such alterations in diet as I have mentioned.

There is probably no fact that is more widely recognised in this portion of the globe, than that mental irritability and depression are relieved by the smoking of tobacco, and if we look up tobacco in a system of therapeutics we find that it is classed with the depressomotors, *i.e.*, with the drugs that diminish muscular power and enfeeble the heart, and among drugs having a similar action it is interesting to note that ipecacuan and antimony have a similar power in relieving migraine. Now, how do they act? It seems to me that tobacco relieves mental irritability and depression, not so much by relaxing the arterioles, though its effect on the muscles may also do something in this direction, as by weakening muscle power generally, and especially that of the left ventricle of the heart, it thus reduces arterial tension and relieves the intra-cranial circulation, and we know that if tobacco is pushed beyond the stage of mental well-being it may cause nausea, and very serious depression or syncope.

My observations on the effects of tobacco smoking on the pulse seem to show that it lowers arterial tension, and quickens the rate of the heart's action, and it is easy to understand that in accordance with Grashey's observations[1] (see p. 123) it will in this way increase the volume of blood passing through the brain, and so produce well-being; and this well-being produced by tobacco is not accompanied by a desire for activity and a feeling of tone in the muscles, but rather by slight languor and disinclination for exertion.

[1] *Fest-Schrift München* (J. F. Lehmann), 1892.

Having taken the view that, in accordance with the above facts, mental depression bears exactly the same relation to the excretion of urates that headache does, and that the causation of the one differs from the causation of the other merely in degree, I was much interested to be told by one of my patients (a man of conspicuous mental ability, who had all his life suffered from mental depression), that when he had his worst attacks, which were always in the early hours of the morning, he was accustomed to obtain relief by sitting upright in bed, in exactly the position that I have to assume in my headache; and the fact is not only interesting as a parallel, but it proves, I think, that in this case the mental depression was not due either to feeble heart or to cerebral anæmia, and taken along with my argument about the effects of tobacco and cardiac depressants, explains the frequent association of high arterial tension with mental depression, because, as we now know, they are cause and effect.

I do not doubt that mental depression may be due to a weak heart, and consequent cerebral anæmia, but such depression would pay little or no attention to fluctuations in urate excretion, and would be benefited rather by lying down than by sitting up.

It is interesting also to remember that in mental depression associated with high arterial tension, digitalis does harm. I have several times given it in cases where there seemed to be a doubt as to the power of the heart, and have seen cases where others have done the same, and the only result was to make the depression worse.

One can easily understand why this should be so, as digitalis affects both factors in the causation of high tension: it strengthens the heart and contracts the arterioles. On the other hand, where mental depression is associated with real cardiac weakness and low tension, digitalis may do a great deal of good.

The relation of these depression attacks to the early morning hours and the similar relation of melancholia to these hours (see "Proceedings of the Medical Society of the State of Pennsylvania," June, 1890), are of great interest in connection with the large excretion of urates and scanty urine, which characterise these same hours in physiological conditions, and I look upon the pathological condition as a mere exaggeration of the physiological.

An extremely interesting case illustrating some of these points

is published by Dr. Willoughby Gardner in the *Lancet* (1891, vol. i., p. 1,311), and with regard to this I think it is not too much to say that I can explain completely every symptom he mentions, and if a case had been manufactured to suit my theories it could not have been better done.

A patient suffers from gout attacks and gouty dyspepsia. On March 3, 1891—he has acute gout in the left foot. From this he recovers two or three days later, considers himself well, and proposes to return to work.

On Sunday, March 8, he attended three long religious services, and took no exercise. On the morning of March 9, he was suffering from acute melancholia of a religious type, with delusions and threats of suicide. Pulse weak, but artery full between beats. Heart, second sound in second right intercostal space loud and ringing.

He was given a mercurial purge and a mustard blister to nape of neck.

In the middle of the night he was seized with a slight attack of gout in the left foot (the same foot as before I remark), and "at once all depression completely disappeared," the pulse felt stronger, and the radial artery could not be felt between the beats, the second sound of heart no longer accentuated or loud.

The case in terms of uric acid causation would read as follows:—Gout, alternating with dyspepsia, cure of an acute attack of gout, some dyspepsia, and uricacidæmia. While this is going on he sits out three long services in a cold church, and takes little exercise. This produces minus skin activity, a rise of acidity, and some retention of uric acid. Next morning, in the alkaline tide, the uricacidæmia returns reinforced by the amount retained on the Sunday. This contracts the arterioles and raises arterial tension, and this in turn produces such an altered circulation in the brain that melancholia with delusions results.

A mercurial purge is given, this clears the blood of uric acid, driving it into the liver, spleen, and joints, especially its old friend of previous attacks, the left foot, and produces a gout attack in the night, and at the same moment, the blood being cleared of uric acid, the pulse alters its character, the melancholia due to the effects of high arterial tension on the cerebral circulation clears up completely. Mercury here acts justs as a dose of iron, lead, or even lithia would have done, and for the same reason,

for urate of mercury, like calomel and other salts, is very insoluble, so that the urate of mercury tends to be deposited especially in those joints where previous attacks had left some urate to attract it. (See p. 35.)

It would be difficult to find a case which more completely illustrates my main points than that narrated by Dr. Gardner.

I should be quite ready in such a case to undertake to produce either gout or melancholia to order, and in other cases similar effects can be produced proportional to the amount of urate that is in hand, and can be acted on.

So far we have been talking of depression or fatigue of mind, but I believe that fatigue of body has a similar if not identical causation. If, as we know well, bodily strength and power of endurance are increased by drugs like opium and cocaine, which produce a free circulation and metabolism in the nerve centres and in the muscles, then obviously the conditions which hinder the circulation and diminish the metabolism in these important structures will produce fatigue of body as well as depression of mind.

As a good deal has been written on this subject lately, it may be of interest to go into it further, and it will form also a prelude to what I shall have to say about the more important effects of uric acid on metabolism and nutrition in future chapters. And, first of all, I will give a figure showing the effects of exercise and perspiration on the excretion of uric acid.

In fig. 28 we see that exercise and perspiration on the 13th of August produced an immediate fall of acidity, and that this produced its usual effect, a plus excretion of uric acid on the 13th, and also on the 14th, for though the acidity rose again on the 14th it did not rise till the largest excretion of uric acid for the day (in the alkaline tide) was over. We have then, as the result of the exercise on the 13th, the passage of an excess of uric acid through the blood on the 13th and 14th, and not only so, but this excess of uric acid affected the arterioles and diminished the excretion of water from the kidneys, so that in this, as in so many other figures, we see that the excretion of urinary water is inversely as the excretion of uric acid. No doubt part of the low excretion of water on the 13th is to be accounted for by the loss of fluid in perspiration, but this would apply less strongly to the 14th when the excretion of water was still lower, and that

this at least was not all due to want of fluids in the body is evidenced by the sharp rise of water on the 15th as the uric acid came down.

We have, then, as the result of this exercise and perspiration, a marked fall of acidity which brought a lot of uric acid through the blood, which in turn affected the arterioles and diminished the circulation through all the organs and tissues of the body. In

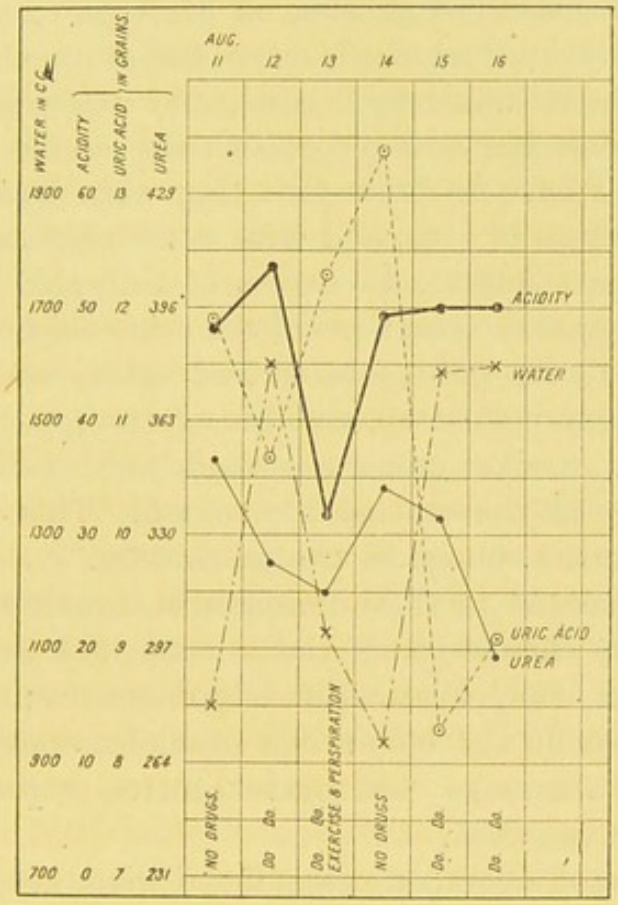

FIG. 28.—CURVES SHOWING THE EFFECTS OF EXERCISE ON THE EXCRETION OF URIC ACID.

this way exercise produces uricacidæmia, and uricacidæmia interferes with the circulation and nutrition of the muscular and nervous tissues producing fatigue. As we shall see presently, the signs of fatigue are but little more than the signs of uricacidæmia; and the fact that exercise produces uricacidæmia explains Cullen's observation, which I have often quoted, that gout seldom attacks persons employed in constant bodily labour, for such persons are constantly excreting excess of uric acid, in place of retaining it in their joints.

I will now shortly mention a case of slight fatigue (that of Weston, the pedestrian), the signs of which have been carefully recorded by the late Dr. Mahomed (*British Medical Journal*, March, 1876), with the object of showing that these signs and symptoms are practically those of uricacidæmia. Thus it is recorded of March 10 and 11 that he lost weight, that he became sleepy, that his pulse tension "was now very considerably increased," that there was a coincident fall of temperature. "His hands felt cold instead of glowing as heretofore; he complained of feeling chilly and required more bed-clothes. The second sound of his heart was accentuated, and the first a little prolonged." Anyone can now recognise these as the signs of uric-acidæmia, and I have no doubt that they were accompanied by a fall in the excretion of urea, and were contemporaneous with and for the most part due to, an excess of uric acid in the blood. They are the common symptoms of the uric acid headache.

On March 12 the pulse tension had again become low; with this his temperature went up, and his extremities became warm. "After this he awoke much refreshed, and continued to walk well and easily to the end of the match. This probably was coincident with the change in arterial tension."

I quite agree as to these changes of condition being coincident with the change in arterial tension, but they were much more than that, they were absolutely due to it; once uric acid was cleared out of the blood the arterioles were relaxed, the nutrition of the muscles and nerve centres improved, and the signs of fatigue vanished.

One of Weston's competitors suffered more severely from the same symptoms, having probably a more severe and prolonged uricacidæmia, and had to give up the match.

Among other symptoms of this condition specially mentioned are a feeling of weight and discomfort in the præcordia, cough with increased secretion of bronchial mucus, and albuminuria. The pulse then requires much pressure to develop it "on account of the fulness of the artery," in other words, high tension.

Cases in which fatigue is fatal, as in that about which a paper was read by Dr. Dukes at the Royal Medical and Chirurgical Society, May 9, 1893 (see *Lancet*, vol. i., 1893, p. 1136), present, I believe, but a mere exaggeration of the above named symptoms, and even the disintegration of the blood mentioned by the last

named observer may be but a further stage of the blood changes which may produce the albuminuria noticed by Mahomed, or the blood changes in anæmia, of which I shall have to speak presently, or the still more marked changes in the blood seen in paroxysmal hæmoglobinuria, which I believe to be paroxysmal uricacidæmia.

But if fatigue is due to uricacidæmia and the contracted arterioles and deficient circulation in important structures which it brings about, it, just as in the case of mental depression, should be proportional to the amount of uric acid in the blood. And the amount of uric acid in the blood is proportional to two things: (1) the amount of uric acid in the blood available for solution in the blood, and (2) the importance of the fall in acidity which increases the solvent powers of the blood.

Now other things being equal the fall in acidity will be greater the greater the perspiration, and perspiration will be greater in hot weather than in cold, and greater also for the same exertion in a man who is not in training as compared with a man who is. Hence fatigue is greater in warm moist weather as noticed by Dr. Dukes, and those not in training will have more uricacidæmia and break down sooner than those who are.

But we have seen in chapters iii. and iv., that the uric acid in the blood is to a certain extent proportional to the amount swallowed in the food, and that those swallow most who live on butcher's meat and other animal foods, while those who are vegetarians swallow probably much less. (See also chapter xvii.) This may, I think, in part account for the reported victory of the vegetarians in a long distance walk which recently excited some interest. (*Lancet*, vol. i., 1893, p. 1396).

The fact that fatigue means an excess of uric acid in the blood (uricacidæmia) suffices to explain at once its relation to acute rheumatism. Let there be exercise and perspiration with increased alkalinity of the blood and uricacidæmia, and let there supervene on this anything such as cold or fever which causes a sharp rise in the acidity of the urine and an equally marked fall in the alkalinity of the blood, and we have all the factors in the natural causation of acute rheumatism.[1] The sharp fall in alkalinity will drive all the uric acid out of the blood into the joints, and the

[1] See also Dr. A. S. Eccles, *British Medical Journal*, vol. i., 1891, p. 1075.

effect on the joints will be proportional to the amount of uric acid in the blood and the rapidity with which it is driven out, and, as I have said, nature's methods in this matter can be imitated to any required extent.

But there is another fact with regard to the causation of fatigue for which I can answer as the result of repeated observation, and this is that if you take care to remove the available uric acid before beginning the exercise, almost an unlimited amount of exercise with perspiration may be undertaken without fatigue.

In fig. 4 is seen the effect of taking salicylate of soda for several days in clearing out uric acid, and also the very marked way in which, when the drug is left off, the uric acid falls, and is for several days far below urea. Under these circumstances, when there is no available uric acid, very considerable exercise and perspiration may be faced without their producing any noticeable fatigue.

This reminds me of another point, namely, that when one is somewhat out of training and has taken rather severe exercise there will probably be some stiffness and myalgic pain on the evening of the same day and subsequently. Now I have frequently noticed that the taking of a little salicylate of soda completely prevents this pain and stiffness; I have little doubt their causation is identical with that of acute rheumatism just mentioned, and that salicyates do good in both cases by holding the urates in solution.

In conclusion, I will merely say that I believe fatigue is uricacidæmia, and that it is proportional to the amount of uric acid which exercise can bring through the blood.

It is open to anyone to repeat my experiment mentioned above, or they can intentionally increase the amount of available uric acid, and so increase the fatigue that results from any given amount of exercise, and I doubt not that if they will do this they will obtain sufficiently conclusive results.

Several of those who spoke in the debate on Dr. Dukes' paper (*Proceedings of the Royal Medical and Chirurgical Society*, May 9, 1893, and see also *Lancet*, i., 1893, p. 1136), spoke of the possible causation of the symptoms by poisonous products in the blood, and this also appears to be the opinion of Professor Foster. (See *Lancet*, i., 1893, p. 1457.)

I am now suggesting that the poison is uric acid, and that its

effects will enable us to account for every symptom and pathological relationship of fatigue. But fatigue pushed to extremes produces syncope, and this syncope may continue and end in death as in the case recorded by Dr. Dukes.

And the causation of this syncope is, as we have seen, that, from causes which differ from physiological conditions merely in degree, the blood is flooded with uric acid. This contracts all the arterioles and capillaries, hinders the circulation through the muscles and nerve centres and the lungs (see chapter ix.), and also produces high arterial tension and alteration of heart sounds as in the case recorded by the late Dr. Mahomed.

If the uricacidæmia gets more severe the heart falters and flutters, as I have noticed that it does under these circumstances in myself (see fig. 25), and finally, if there is no relief it stops, and syncope supervenes. Speaking of dilatation of the heart, Sir W. H. Broadbent says: "It is usually gradual in its development, but acute dilatation of the heart is a more common occurrence than is generally supposed, *and when it is induced by effort antecedent high arterial tension is, according to my experience a constant predisposing factor.*" ("The Pulse," p. 168.)

But if the syncope of fatigue has this causation it seems very probable that syncope met with under other conditions may have a similar causation.

I have already (chapter vii.) mentioned the pulse of epilepsy and other convulsions, its slowness and high tension, and the late Dr. Moxon's suggestion that stoppage of the heart is the cause of the fits, and I would further point out that my own experience seems to show that the heart specially flutters and gives signs of discomfort as the tension rises, that is to say, as there is a change from low to higher tension. I have also mentioned the syncope of bathing. There is another condition in which syncope is not uncommon, namely, convalescence from acute disease, and here also it is associated with high arterial tension and subnormal temperature. I make it a rule not to allow any convalescent to sit up or make any exertion till the temperature has risen to normal and remains there, for I believe, and indeed I know, that their heart is often affected, perhaps dilated by the high tension, and that any effort may be the last straw.

And there is one other condition in which syncope sometimes occurs, namely, during or just after the administration of chloro-

form, which seems to me to have many points in common with the conditions named above, though as I have no personal experience worth mentioning, anything I say must be taken as suggestive merely.

What I would suggest is this, that chloroform relaxes the arterioles and lowers arterial tension (as appears to be well known), and I think that it may do this like so many other drugs mentioned in this volume by clearing the blood of uric acid.

Then when the chloroform is left off there will be a rise of arterial tension which I have spoken of in the case of other drugs as the rebound, and if this is great and rapid the heart will flutter and falter, and perhaps cease to beat.

Further, the fluctuation in arterial tension which the drug produces will be greater (other things equal) the more uric acid there is in the body and blood at the time it is administered, and the greater the fluctuation the greater the strain on the heart.

Taking this view of the matter, I was greatly interested by an article by Dr. R. Kirk, in the *Lancet*, vol. ii., 1893, p. 429.

In this paper he shows that in animals when inhalation of chloroform is discontinued the lungs are emptied of its vapour in 10-20 seconds, and a little after this the heart suddenly slows and becomes irregular, and there may be syncope. Further, the longer the inhalation is continued, the later does this slowing and irregular action of the heart appear, and he says, "the irregular action commences when the last drop of chloroform has left the blood."

This disposes once and for all of any idea that the irregular action is due to the cholorform, but if it is due to the rising tension as I am suggesting, it is just what we should expect —indeed it almost amounts to a demonstration.

If the heart fails rapidly its action may become quick instead of slow, just as in other conditions where there is high tension. (See chapter v.)

And then with this failure of the heart the blood pressure will fall very greatly; but that there is rising arterial tension at the onset of the trouble is I think proved by the slowing of the pulse, in accordance with Marey's law. (See chapter v.) While if the first event is a great fall of blood pressure, as Dr. Kirk seems to suppose, there is no reason why the heart should slow, and I have just pointed out that arterial tension is high and the pulse

slow in the parallel conditions of fatigue, convalescence (post febrile bradycardia), and certain cases of epilepsy.

Now post chloroformal high tension differs from these chiefly in its rapid onset, and it is on this account likely, as my experience seems to show, to affect the heart more severely.

Further evidence pointing in the same direction is, I think, to be seen in the fact that nitrite of amyl is useful in this chloroform syncope, and there is probably no drug which would more quickly relax the arterioles and prevent the rise of tension; while it is hard to see how it can do good if the tension is already low.

The above cardiac failure is accompanied by violent struggling or even convulsions on the part of the animal or patient, and we are here brought again into touch with my explanation of the pathology of convulsions from rising tension, in the previous chapter.

When struggling occurs in the course of inhalation it is, I think, the practice of anæsthetists to give chloroform more freely for a little, and this is, it appears, the best thing to do, for the trouble is due to failure in the supply of chloroform allowing the tension to rise.

Then if the tension effects of chloroform are due to its action on uric acid, and proportional to the amount of this substance to be met with in the blood, we can again see several facts which admit of easy explanation. Thus it has, I believe, been suggested that there is more trouble with chloroform in London than in Edinburgh, and again we know that gout is common in London and rare in Edinburgh, and there will probably therefore be more uric acid in the former than the latter; similarly, the vegetarian natives of India may have some immunity from chloroform syncope as compared with beef-eating Englishmen.

I am aware that it was suggested in an annotation in the *Lancet* (vol. ii., 1889, p. 606), that gout might account for the different reaction to chloroform in Edinburgh, London and India respectively, but no explanation was given of the way in which it acted.

I have already (chapter v.) quoted from Marey the fact that alcohol causes a dicrotic pulse, except when it is accompanied by gastric disturbance; and the said gastric disturbance, by keeping up the alkalinity, prevents the alcohol clearing the blood of uric acid.

I think also that the alcohol or morphine, which are so often advised to be given before inhalation of chloroform, may act by clearing the blood of uric acid, and thus preventing a rebound when the anæsthetic is left off. If there is no uric acid in the blood when the chloroform is given there will be no great change of arterial tension either when it is begun, or when it is left off.

The rebound after alcohol or morphine comes more gradually, and will therefore affect the heart less severely.

Then, in a recent interesting address, Dr. Lauder Brunton remarks that he has been told by Professor Poehl, of St. Petersburgh, that in Russia the presence of an excess of alkaloidal substances in the urine is regarded as a sign that it will be dangerous to give chloroform (*Lancet*, vol. ii., 1893, p. 861), and mentions that he himself had previously entertained the idea that certain alterations in tissue change might increase the danger of chloroform.

There can, I think, be no doubt that an excess of uric acid in the blood produces very great alterations in tissue change, and I suspect that the excess of alkaloids noticed by the Russian observers runs parallel with an excess of uric acid. (See chapters viii. and x. to xiv.)

I have often been struck with the fact that the conditions in which increased toxicity of the urine is described are very frequently conditions in which my experience tells me that there must also be an increase of uric acid in the blood and urine; and I would suggest that the quantity both of uric acid and of alkaloids should in future be observed in the urine before operations under chloroform.

Thus after pneumonia and also after typhoid fever the toxicity of the urine is said to be high (*Prog. Med.*, April, 1889, pp. 277 and 296), and after both there is an excessive excretion of uric acid, and all the signs of its excess in the blood.

As to the way in which an excess of uric acid in the blood may produce these alkaloids, see as regards the intestines, chapter vii., and the causation of oxaluria, chapter xii., and I think there can be very little doubt that a deficient circulation produces a similar effect in the tissues generally. Now Professor Mosso tells us, with regard to the pathology of fatigue, that when it is carried beyond a moderate amount the blood is subject to a decomposing process through the infiltration of poisonous substances into it.

(See *Lancet*, vol. i., 1887, p. 1295.) There is, I think, no doubt that the blood in fatigue contains an excess of uric acid, and owing to the effects of this on metabolism, other poisons (sulphuretted hydrogen, &c.) will soon be added. (See also chapter xii.)

Another writer tells us that the proportion of alkaloids in the urine during the eight hours after waking is five times as great as in the urine of the rest of the day. (*British Medical Journal*, vol. ii., 1886, p. 1271.) Now the largest excretion of uric acid and the most marked uricacidæmia occur in these same hours.

Diagnosis of mental depression due to uric acid depends chiefly on the fact that it is proportional to the uric acid in the blood and fluctuates with it; that, as pointed out by Professor Lange, it is periodical, in which also it resembles the headache and fits due to the same cause. Being directly due to the high arterial tension which uric acid produces it is made worse by anything which raises arterial tension, and better by anything which reduces it.

Fatigue, again, is to be diagnosed from its fluctuating in accordance with the amount of available uric acid.

The indications for treatment are practically the same as those for the uricacidæmia of headache, bearing in mind that uricacidæmia which produces mental depression is very often secondary to other conditions, such as dyspepsia, debility after parturition, prolonged lactation, or fevers, or accompanying the progress of new growths or other organic disease; and it is useless to treat the uricacidæmia without paying attention to its cause, though in any case diminishing the intake of urates will probably do some good, for the more the available urate the greater and more lasting, as we have seen, is the interference with metabolism and nutrition.

CHAPTER IX.

Asthma and Bronchitis.

Before I attack the special subjects of this chapter I will say a few words about what is called a common cold. My point with regard to it is this—how far is a common cold due to changes originating within the body, how far is it due to external agencies?

We all know that a cold may run through a whole house; in this case in so far as B's cold was due to proximity and contact with A, it was due to agencies entirely external to his (B's) body. But there are obviously other factors, for B does not always get A's colds; on the contrary, it is only when he is a little out of sorts, when he suffers from dyspepsia, or other small causes of trouble, that he is liable to get them; at other times when he is in perfect health he may entirely escape.

Again, it is common experience that women are specially liable to take cold at their menstrual period, when they are also more liable to dyspepsia, gastric upset, bilious attacks, &c.

It is, I think, therefore evident that in a common cold we have two factors, (1) altogether external to the body, and (2) originating in certain disturbed conditions of digestion, nutrition, and metabolism inside the body. If 1 does not coincide with 2 no disease results.

Something of this sort, is I think, intended by Dr. H. Alston, who, in an article in the *Lancet* (vol. ii., 1893, p. 807), says: "I was called to see a child, aged 3 years, suffering from slight fever, with a few râles audible on auscultation over the large bronchi and rapid respiration;" and then he goes on to say that these

symptoms disappeared in two cases after a purgative was given, and it is evident from the context that he considers that the slight bronchial trouble is due to some primary intestinal derangement which the purgative removes.

Then, again, I think it must be common experience that a cold in others besides children is often greatly improved, or, if treated early even cured, by a good purge. In a word, I believe that the internal condition which allows the external factor to act is often some intestinal condition which is put right by a purge. Similarly, a dose of wine negus, or of spiritus ammon. aromat., and sp. æther nit., or of pulv. ipecac. co. at bed time have cured or cut short many a cold. They all clear the blood of uric acid, and allow the arterioles throughout the body to relax.

I hope that in what I have to say about bronchitis and asthma we may get an insight into the nature of some of these internal conditions, and the way in which they may favour the onset of a common cold.

Several years ago, in a paper in "Wood's Medical and Surgical Monographs" (New York, February, 1890, p. 359), I said with regard to asthma: "Here, again, we have a possibly functional disorder which, like so many I have mentioned, has long borne a somewhat indefinite relation to gout, and it has occurred to me since my investigation on uric acid has brought to my notice its action on the arterioles, that directly or indirectly it may affect the circulation in the bronchi and lungs and so produce asthma. There are also not a few points in the history and symptoms of asthma, and the onset of the attack, which may be taken as pointing to its possible origin in a uric acid storm."

I have also mentioned elsewhere several things which seem to make it probable that uric acid affects both the pulmonary and the system circulation in the same way.

My interest in the matter was also greatly quickened by seeing in the *Lancet*[1] a notice of a paper by Dr. Yavein, of St. Petersburg, in which it appeared that rge doses of citrate and carbonate of soda diminished the excretion of water from the skin and lungs, for I already knew that similar doses of these alkaline salts would, by increasing the uric acid in the blood, contract the vessels in the kidneys, and diminish, so long as the excess of uric acid might last, the excretion of water in the urine.

[1] *Lancet*, vol. i., 1882, p. 329 and 882.

It seemed probable, then, from these considerations that uric acid, not only affected, as I already knew well, the vessels of the kidneys and skin, but Dr. Yavein's results made it probable that it affected also the vessels of the lungs and diminished the output of water from them, and as soon as I was able to I began some researches with a view to confirm Dr. Yavein's results, of which I shall speak presently.

Asthma is commonly spoken of as a paroxysmal affection, attacks coming suddenly about 2 a.m. to 4 a.m., when the sufferer has gone to bed quite well. The dyspnœa is expiratory, and is supposed to depend on a morbid condition of the very small bronchial tubes; and this morbid condition is supposed to consist of hyperæmia or congestion, with or without the addition of a certain amount of muscular spasmodic constriction.

Now asthma has been called by Dr. Goodhart[1] and others a "paroxysmal neurosis," and they would, I suppose, probably class migraine and epilepsy in the same category; but I have shown[2] that many cases of migraine and epilepsy are entirely due to the changes which uric acid produces in the circulation of the nerve centres, and that if the blood is kept clear of this poison the attacks will practically cease to recur.

And my researches leave little or no doubt in my mind that asthma represents one of the effects of uric acid on the circulation in the thorax, and that it is paroxysmal for the same reason that migraine and epilepsy are paroxysmal in accordance with the natural fluctuations in the excretion of uric acid, and the amount of the substance passing through the blood; and we shall see further on that clearing the blood of uric acid and keeping it clear is the only point requiring attention in the treatment of asthma, and that all drugs which experience has shown to be useful in this disorder have this effect, or else directly reduce the high arterial tension which uric acid produces, and further, they are almost all equally useful in migraine and epilepsy.

We now come more directly to the relationship of the asthma attack to the excretion of uric acid.

And one of the first things which directed my attention to this matter was the very similar effects of diet both in migraine and asthma. It will be remembered that I was myself a sufferer

[1] *British Medical Journal*, vol. ii., 1891, p. 254.

[2] *Brain*, Spring and Summer Number, 1893, p. 230.

from migraine, that when I was on ordinary meat diet I used to have about 30-40 attacks in a year, that when I was on extra meat diet for purposes of training at Oxford (and it now appears to me that this was indeed a very dangerous process) my attacks were both more frequent and severe, while now, when I take no meat at all, they are practically absent altogether ; and I therefore learned with great interest from a fellow student of my own (the late Dr. W. E. Steavenson) that his asthma attacks had been affected in exactly the same way by the training he had done at Cambridge. He suffered also from eczema and bad headaches, and had had acute rheumatism, and his pulse was often slow and of high tension.

Then I have myself had attacks which, if not strictly asthmatic, are undoubtedly closely related to it, and before I recognised this relationship they used to cause considerable uneasiness in my mind by suggesting more serious disease.

Thus I noticed that occasionally in the early morning before breakfast I had a feeling of heaviness or tension behind the sternum, with a little wheezing in the chest, followed by the expectoration of a little mucus ; I also noticed that the pain invariably disappeared soon after breakfast, though both the pain and wheezing occasionally returned about 5 or 6 p.m., to disappear again after dinner.

What specially struck me was the comparative suddenness with which the pain came and went, and the fact that there were no signs of catarrh whatever at other times of the day.

Some time after this, in the course of an experiment undertaken for other purposes, I purposely increased very greatly the excretion of uric acid and the amount passing through the blood ; and I found rather to my surprise that my chest pain and troubles were very decidedly worse during this experiment, and when, later on, I reversed the process and cleared the blood of uric acid, so that there was but a very small excretion for several days, my chest troubles completely and suddenly disappeared and remained absent for some time, till one or two meat and wine dinners with friends increased the uric acid once more and brought back a morning wheeze.

This opened my eyes to the real nature of my trouble, and I was at once able to explain its periodicity : for, as I have pointed out, the largest excretion of uric acid occurs in the early morning

hours before breakfast, and the next largest in what I have spoken of as the afternoon alkaline tide, from 3 to 6 p.m.

Again, the onset of the attack in the early morning hours, just when the acid tide of the night is coming to an end, and the excretion of uric acid is rising, the fact that it tends to be better in winter, when, as I have shown, the excretion of the uric acid is low, and worse in the spring and summer,[1] when the excretion is high and rising, are points in which it resembles migraine, mental depression, and other troubles due to uric acid.

Then again, as pointed out by Dr. West,[2] the attacks come soon after meals, and meals nearly always increase the alkalinity of the blood, and the amount of uric acid it holds in solution.

I mentioned above that my own asthmatic symptoms were better after breakfast, for though breakfast does increase the excretion of uric acid, the largest excretion in the whole 24 hours generally takes place in the early morning hours before breakfast, and any rise of excretion caused by breakfast generally comes to an end, in my own case, about 11 a.m.

Dr. West (previous reference) considers that the attacks are due to a poison circulating in the blood, and I have no practical doubt that this poison is uric acid.

Asthma, again, tends to be better during pregnancy unless there is much vomiting, and this is easy to explain, for pregnancy entails a general increase of metabolic activity, which results in a rise of urea, and a corresponding rise in the acidity of the urine and a correlative fall in the alkalinity of the blood, which is now no longer a good solvent of uric acid, so that it contains but little of it; it is easy to understand, on the other hand, how vomiting will reduce urea and acidity, increase the alkalinity of the blood, and flood it with uric acid.

In this relation to pregnancy asthma is the exact parallel of migraine and Raynaud's disease, for both these kindred troubles are better or cease during normal pregnancy, but return when it is over (p. 221).

I have been told by several sufferers, among others by the late Dr. Steavenson, that the asthma attack is often followed by a diuresis. Here again the parallel with migraine, epilepsy and Raynaud's disease is absolute; and this fact proves to my mind

[1] See *Progrès Médical*, January, 1890, p. 73.

[2] *British Medical Journal*, vol. ii., 1890, p. 1123.

not only that the arterioles are relaxed after the attack with a low excretion of uric acid in the urine, but also that they were contracted during the attack, causing a retention of water in the body, which takes the first opportunity of passing off as soon as they are relaxed at the end of the attack.

But I have shown that the urinary water is from day to day and hour to hour inversely as the uric acid excreted along with it, *i.e.*, with high uric acid you get low water, and *vice versâ*. The excess of uric acid in the urine is the index of a similar excess in the blood, and the excess of uric acid in the blood contracts the arterioles all over the body, among others, those of the kidneys, preventing the outflow of water. (See *Journal of Physiology*, vol. xiii., and *Lancet*, July, 1892.)

The fact, then, that the attack of asthma is followed by a diureses proves, just as in the case of headache, epilepsy and Raynaud's disease, that the attack was accompanied by a plus excretion of uric acid, with high arterial tension and scanty urine.

There can, then, I think, be no doubt about the relationship of the asthma attacks to a large excretion of uric acid in the urine, or to the high arterial tension which its excess in the blood produces, and we shall see other reasons for this opinion further on.

With regard to the researches of Dr. Yavein, showing that alkalies diminish the output of water from the lungs, I have made some experiments, comparing the excretion of water from the kidneys with that from the lungs in a given time.

I knew that I could control the excretion of water from the kidneys by acting on the uric acid in the blood, and increasing or diminishing its quantity; and I argued that if alkalies which diminish the urinary water by increasing the uric acid in the blood, diminish also the excretion of water from the lungs, then I ought to be able to control the excretion of water from the lungs as well as that from the kidneys, and my researches, so far as they go, seem to show that, to a certain extent, this is the case.

I began to investigate the matter in the following way: I measured the urine passed in 15 minutes, and estimated by means of tubes filled with calcium chloride the water from the lungs in 5 minutes, generally in the middle of the 15 minutes in which I estimated the urine; I then divided the urine passed in

15 minutes by 3, and compared this with the water given off in 5 minutes from the lungs. (See chapter xviii.)

I followed first of all the natural fluctuations in the urinary water, and then proceeded to produce fluctuations by means of drugs affecting the uric acid.

In Carpenter's "Physiology," ed. viii., p. 412, it is stated that from 7-11 oz. of water is daily thrown off from the lungs, the exhaled air being saturated with water, or nearly so. The quantity varies with the rapidity of respiration, with the stage of digestion, and rest or activity, etc.

Taking the quantity as 11 oz., and the urine as 52 oz., we get a relation of 1 part of water from the lungs to 4.7 parts by the kidneys.

The results I shall now mention were obtained generally about the same hour of the day and at rest, so as to eliminate as far as possible the effects of digestion and of exercise.

1893. Date.		In five minutes. Water from Lungs. grams.	Water from Kidneys. cc.	Relation.
Feb.	1	1.169	4.5	1-4.8
,,	2	1.497	7.0	1-4.6
,,	3	1.514	6.0	1-3.9
,,	4	1.560	6.1	1-3.9
,,	8	1.670	7.3	1-4.3
,,	10	1.367	6.0	1-4.3
,,	17	1.310	5.6	1-4.2
,,	18	1.466	6.3	1-4.2
,,	18[1]	1.515	7.6	1-5.0
May	10	1.186	4.6	1-4.1
June	8	1.190	4.3	1-3.9
,,	9	1.370	4.3	1-3.1
	Total	16.814	69.6	1-4.1

[1] Two consecutive experiments.

I also made similar experiments on ten other days at times when the urine was very profuse, as from 10-18 cc. in the 5 minutes, and in none of these did the water from the lungs rise to a corresponding extent, probably because the expired air was saturated and no more water could therefore be given off by the lungs; and on these days one got relations of 1-10, 1-12, and even 1-14. That is to say, for obvious physical reasons, the water expired from the lungs cannot rise beyond a certain point.

From the figures given in the foregoing table it is seen that the total excretion from the lungs was 16.8 grams, and from the kidneys 69.6 cc., giving a relation of 1-4.1, a difference of six points in the first place of decimals from the relation obtained from the above-quoted work on physiology. If in the same table we take the highest excretion from the lungs, 1.67 grams, the corresponding excretion from the kidney is 7.3 cc., the lowest from the lungs is 1.16, and the corresponding kidney excretion 4.5 cc. Then the highest excretion from the kidney is 7.6 cc., and the corresponding excretion from the lung 1.5 gram; the lowest from the kidney is 4.3 cc., and the corresponding excretion from the lung 1.1 gram.

Thus it appears that within the limits imposed by the physical laws which govern the saturation of the atmosphere with moisture, the excretion of water from the lungs does vary on parallel lines with the excretion of water from the kidneys with a relation of 1-4.1 to 1-4.7, and those things that increase the excretion of water from the kidneys will also increase the excretion of water from the lungs within these limits.

My research, then, seems to show that Dr. Yavein's observation was quite correct, and that an alkali which diminishes the water from the kidneys (see p. 101), so long as it increases *(but only so long)* the uric acid in the blood and urine, will at the same time diminish the excretion of water from the lungs to a corresponding extent.

Having found, then, that the water exhaled from the lungs varies with the water excreted from the kidneys within certain limits, we must consider the probable cause of this parallelism of the two excretions.

I have said above that in everyone from hour to hour and from day to day the excretion of water from the kidney varies in the reverse direction with the excretion of uric acid; and so constant is this law, that by controlling the excretion of uric acid I can control the water with a certainty that is little short of absolute; and in clinical work if the water is known from day to day, the uric acid, greater or less, can be calculated from it with considerable certainty (see *Lancet*, July, 1892, and elsewhere); and not only so, but all the important drugs (mercury, opium, salicylates, iodides, caffeine, &c.) which cause diuresis do, as I have shown, diminish the excretion of uric acid at the time

of the diuresis, or, as I put it, they cause a diuresis by clearing uric acid out of the blood and enabling the vessels of the kidney to dilate, because the contraction of the arterioles throughout the body varies directly with the amount of uric acid that is circulating in the blood. (See *British Medical Journal*, February, 1889.)

But in the uric acid headache, and other conditions in which there is an excess of uric acid in the blood, not only is the urine scanty and the skin pale, cold and dry, but the saliva also is scanty, and it can be shown (*Brain*, 1893, prev. ref. and ch. x.) that the gastric juice, the bile and the intestinal juices are all equally scanty, and we now see that there is some reason to believe that the excretion of water from the lungs is correspondingly diminished.

And the explanation of this is simple, for the arterioles throughout the body are all contracted by the uric acid in the blood, and if the blood is examined at this time it will be found to contain an excess of water, both hæmoglobin and cells being relatively diminished.

We have arrived then at this point, that uric acid which contracts the arterioles and capillaries throughout the entire systemic circulation, and diminishes all the excretions, affects also the vessels of the lungs and diminishes the output of water from them to a corresponding extent.

What is the bearing of these facts on the pathology of asthma, a paroxysmal disturbance of function resembling at so many points, as I have shown, migraine and epilepsy and Raynaud's disease, which are also paroxysmal?

As I have said elsewhere, I think it can be shown that migraine, epilepsy and Raynaud's disease are paroxysmal in relation to the fluctuations in the excretion of uric acid and the amount of it that is passing through the blood, migraine and epilepsy representing the effects of high arterial tension on the intracranial circulation, and Raynaud's disease the effects of contracted arterioles on the nutrition of the skin and extremities (ch. xi.).

Asthma appears to be paroxysmal in relation to similar fluctuations of uric acid; is it one of the effects of uric acid on the pulmonary circulation?

Now let us look at one or two points in the anatomy and physiology of the lungs.

We have two circulations going on there: (1) that of the pulmonary artery in which there is comparatively low pressure, and (2) that of the bronchial arteries which come from the systemic circulation, in which there is much higher pressure; and we have these circulations enclosed in a cavity, the pressure in which varies greatly from moment to moment with respiration.

But if you diminish the atmospheric pressure on any vascular area of the body, its capillary vessels at once dilate (see Marey, "La Circulation du Sang," 1881, p. 444), and it seems obvious that most blood will stream into that area which has the highest arterial tension behind it, because it is the pressure in the arteries which drives the blood through the capillaries into the veins (see Marey, p. 321 *et seq.*) It follows from this reasoning that when atmospheric pressure is diminished in the thorax, there will be more congestion in the bronchial circulation than in the pulmonary; and there will be more congestion in the bronchial circulation the higher the tension in the systemic circulation of which it forms a part.

Here, then, we have a tendency to hyperæmia and congestion in the lungs, which is probably most marked in the area of distribution of the bronchial arteries, which will increase on the one hand with rising arterial tension, and on the other with anything that obstructs the free entry of air into the thorax, and so tends to diminish more than usually the atmospheric pressure during inspiration.

It is interesting to note that Marey (prev. ref., p. 448) attributes in no small degree to the diminished pressure in which they have to work, the ease with which the lungs become congested or inflamed.

It seems to me that such a congestion or hyperæmia affecting especially the bronchial circulation may quite account for the retro sternal pain, with slight increase of bronchial secretion and wheezing, which I have myself experienced in connection with excess of uric acid in the blood, and the high arterial tension it produces; and a slight increase of this disturbance may easily account for the bronchial congestion of asthma.

May not something of this kind represent the internal factor in the causation of a common cold, and explain its relation to dyspepsia, menstruation, &c., which, as we know, so often upset the physiological balance, and bring an excess of uric acid through

the blood, producing high arterial tension, and, in the way just explained, hyperæmia or congestion in the area of the bronchial circulation in the thorax?

Do we not here also get a ray of light on the causation of chronic bronchitis, and on its frequent association with chronic Bright's disease and high arterial tension in the declining years of life?

It is exactly in the declining years of life that, owing to failing nutrition, falling urea, and diminishing acidity we get a very large amount of uric acid dissolved out and passing through the blood, and most in those who have taken most freely a highly nitrogenous diet in the previous twenty years of their life.

The uricacidæmia thus brought about contracts the arterioles and raises arterial tension, and the further general failure of nutrition, the chronic Bright's disease, and the chronic bronchitis, are secondary to this; it is little wonder, then, that as pointed out by Professor Humphry, a large proportion of those who attain to great age are more or less strict vegetarians.

It seems probable that once this bronchial hyperæmia has come into existence, the swelling of the mucous membrane may further obstruct the passage of air to the bronchi and alveoli on the distal side of this obstruction, and this will lead to continually increasing fluctuations in the pressure in the distal air passages, with increasing hyperæmia and congestion, so that matters tend to get worse and worse, and the hyperæmia only subsides after it has been relieved by a copious secretion of mucus or a general oozing of blood.

I do not think that an affection of the bronchial area alone will account for the fluctuations in expired water which take place, and believe that uric acid will affect the pulmonary vessels as well as the bronchial, and may possibly do this to the extent of greatly contracting its vessels and rendering the whole lung anæmic; but this is probably a rare condition of affairs, though occurring perhaps in uræmia or other organic disease, and the more common effect of uricacidæmia and high arterial tension is the congestion and hyperæmia in the area of distribution of the bronchial arteries, which I have endeavoured to point out above, and which, when slight and chronic, may lie at the root of chronic bronchitis or the onset of a cold, but when more sudden and severe may produce an asthmatic paroxysm.

If asthma has a causation such as I am suggesting, it will be made worse by anything that contracts the systemic arterioles and raises arterial tension, and it will be made better by anything that relaxes the arterioles and reduces arterial tension. It will also be made worse by anything that obstructs the free entry of air into the thorax.

The most common cause of high arterial tension is uric acid in the blood, and this suffices to explain at once the relationship of asthma to gout and various other diseases, as we shall see.

The relationship of the asthmatic attack to the early morning hours is simply its relation to the largest excretion of uric acid in the twenty-four hours, and the high arterial tension it produces in passing through the blood.

During sleep also the patient is generally in the recumbent position, and this position raises the general arterial tension as compared with sitting or standing (Marey, prev. ref., p. 340), hence a sufferer can sometimes sleep in a chair but not in a bed; though no doubt also position affects the action of the muscles of respiration.

I have spoken above of the relationship of asthma to diet and to meals, and these are quite easily explained by their effects on the uric acid in the blood, and not a few of the minor premonitory symptoms of an attack are those of uricacidæmia.

No one who understands the relationship of dyspepsia to migraine and epilepsy will have any difficulty in understanding its relationship to asthma. In all cases, however, the relationship is a double one. Dyspepsia is partly a cause and partly an effect, of uricacidæmia and high arterial tension.

There can be no doubt that uricacidæmia when it contracts the arterioles may practically suspend entirely gastro-intestinal digestion and absorption, and allow putrefactive processes to take their place; in this way uricacidæmia causes dyspepsia. (See chapter x.)

But dyspepsia, on the other hand, will also cause or increase uricacidæmia. Suppose there is no excess of uric acid in the blood, but that some indigestible substance as a piece of pork upsets gastric digestion; the result is the more or less complete arrest of digestion and absorption, even if there is no vomiting, and this promptly causes a fall in urea and a corresponding fall in the acidity of the urine, the alkalinity of the blood is increased,

and any uric acid within its reach is at once taken up in solution. Such is the usual causation of a "bilious attack," or uric acid storm, and the high tension which results from the passage of the uric acid through the blood produces either headache or epilepsy, or, if the dyspepsia is chronic rather than acute, mental depression, and leads on to that general failure of nutrition which we call Bright's disease.

I believe that the relationship of asthma to dyspepsia is precisely similar, and in some cases the cure of the dyspepsia is the cure of the asthma.

The relationship of asthma to gout is equally simple, and is shared also by migraine, epilepsy and Raynaud's disease.

Asthma is due to uric acid in the blood and the high arterial tension it produces. When from any extraneous cause, as a blow, a chill, a local irritation, or a rise of temperature, uric acid is precipitated on a joint, the blood is cleared of the excess it previously contained, and the high tension and the asthma subside. An interesting case of this kind is mentioned in the *British Medical Journal*, vol. ii., 1888, p. 954, where it is told of Frederick the Great that he had a severe attack of dyspnœa followed next day by gout. It is further said that he was very gouty and had an irascible temper; this last representing the effects of uric acid on the intra-cranial circulation, just as the dyspnœa represented its effects on the thoracic.

Phthisis and gout are sometimes said to be related (see *Medical Times and Gazette*, vol. i., 1862, p. 499, and *Deutch Archiv. f. Klin. Med.*, b. 47, hft. 5 and 6; also Sir Dyce Duckworth, "A Treatise on Gout," p. 172, where very interesting points are mentioned), and they certainly often occur in the members of the same family, as I have several times remarked. It seems also that they do not both occur at the same time, but alternate, just as asthma and gout do; and I know that this was the opinion of the late Sir Andrew Clark, arrived at, as he himself told me, from personal experience. (See also *British Medical Journal*, October, 1889.)

Now it appears to me that the changes in the pulmonary circulation which uric acid produces may completely account for this. For while a man is eating largely of animal foods, he will have high acidity, his blood will be pretty clear of uric acid, and his pulmonary circulation will be free; but he will have gout, because he is storing and retaining large amounts of uric acid.

Let this man, however, meet with an accident which confines him to bed for weeks and months, so that appetite, digestion and metabolism all run down; with falling acidity the stored urate will pass in excess through his blood, his pulmonary circulation will be more or less markedly deficient, and the bacilli will have their opportunity, and may not neglect it. I believe that such chronic uricacidæmia is a great danger for the lungs.

Uricacidæmia may also be brought about and kept up by dyspepsia and other gastric troubles, hence perhaps the origin of the dictum I have heard at lectures at Brompton with reference to the treatment of early phthisis, "Take care of the stomach, and the lungs will take care of themselves."

A similar explanation may also apply to the cases of acute phthisis following destruction of the mucous membrane of the stomach by corrosive fluids recently recorded by Dr. Soltau Fenwick (*British Medical Journal*, i., 1894, p, 129.)

Phthisis, again, like asthma, is often markedly worse in the spring of the year (see Dr. Barlow, *Lancet*, vol. ii., 1891, p. 285), and iodides are supposed to be useful in cases in which there is a syphilitic taint, but if these drugs keep the blood free from uric acid, and thus allow of a good circulation through the lungs, I should be quite prepared to find that they cure many cases that have nothing to do with syphilis.[1]

Asthma has occasionally been seen to alternate with epilepsy, and this is probably simply due to the fact that some third factor has for a time rendered the thoracic circulation more liable to be upset by the high tension than the intra-cranial; and any temporary interference with free inspiration might, as I have suggested, account for this. (See also a case recorded in the *Lancet*, vol. i., 1893, p. 1383.)

Then, again, the relationship of asthma to eczema and skin diseases is probably simple, for I have pointed out in my writings on Raynaud's disease (see ch. xi.), that not a few skin diseases represent merely the effects on its nutrition of vessels contracted by uric acid; and I have for several years taken this probability as my guide in the treatment of such skin diseases as come under my notice, with results which have often appeared to me to be very satisfactory.

[1] It is interesting to note also that iodides appear to be useful in actinomycosis. (See *British Medical Journal*, vol. i., 1894, p, 61.)

We must bear in mind that such skin lesions are produced in the vascular area, the deeper layers of the skin, and hence may take several days to show much on the surface; meanwhile the high tension which produced the asthma and also the skin troubles may have disappeared, so that the asthma may appear to alternate with the skin trouble, when it is really contemporaneous.

The relationship of asthma to nasal irritation and obstruction may be simply that these tend to diminish the free inrush of air in inspiration, and will thus tend to diminish for a time the atmospheric pressure in the chest, and so increase the congestion in the bronchial area; other things, as arterial tension, remaining the same.

Hay asthma, cat asthma, &c., may, in this way, be due to the irritant action of certain small particles in producing nasal congestion and obstruction, with the concomitant action in the case of hay asthma, of heat, which increases the alkalinity of the blood and the amount of uric acid it will contain.

Then again dust, even in ordinary asthma, will often account for the onset of an attack, as the dust of particular trades, fine particles of hay or straw, the dust of long railway journeys in dry weather, even the dust of unused rooms and old books—all these may act in much the same way, producing first of all nasal irritation and congestion, the bronchial trouble being secondary to the blocking of the upper respiratory passages thus brought about.

Bad air and deficient oxygen may act by increasing the alkalinity of the blood, as I have pointed out that deficient oxidation probably produces a uricacidæmia in this way: hence the headache of badly ventilated theatres, and hot, crowded rooms. (See p. 27.)

Certain odours again may produce more or less nausea, which again will increase the alkalinity of the blood; and shock or fear may have much the same effect, and so precipitate an attack of asthma.

The drug, which of all others has been most widely used in asthma, is probably iodide of potassium, or the iodides; and it is interesting to find that they relax the arterioles and lower arterial tension, which they are well known to do, by clearing the blood of uric acid; and I have been able to show (see chapter iii.) that the fall of arterial tension and the diuresis they produce is exactly

contemporaneous with a very marked fall in the excretion of uric acid, and as every drug which produces a similar fall in the excretion of uric acid, produces also a similar fall of arterial tension and a diuresis, I have felt no hesitation in attributing these effects of iodides to their action on the solubility of uric acid in the blood.

The iodides then probably relieve asthma by clearing the blood of uric acid and so reducing arterial tension, and the resulting congestion in the area of the bronchial arteries: and I have given in my paper on "The Iodides,"[1] a figure to show the effect of Hair's asthma cure on the excretion of uric acid.

Of the action of acids, morphine and the nitrites I have already spoken, showing that they, like the iodides, clear the blood of uric acid.

Bleeding will obviously reduce arterial tension in the systemic circulation, and tobacco and lobelia are cardiac and muscular depressants, and probably lower arterial tension in this way.

Antipyrin, I believe, acts as an acid, relaxing the arterioles by clearing the blood of uric acid; but it may also act to some extent like the cardiac depressants just mentioned, and it seems probable that the fumes of sulphurous acid or of nitre paper may diminish the alkalinity of the blood, and so tend to clear it of uric acid.

These facts leave in my mind no practical doubt that asthma is generally the result of the action of contracted arterioles, and high arterial tension on the thoracic circulation, though as in the parallel case of the intracranial circulation, certain local or general conditions may affect to an important extent the result produced in any given case.

I have also no doubt that the circulatory changes are generally due to uric acid in the blood. (See "International Clinics," vol. iii., third series.)

If these deductions are correct, the indications for treatment are moderately clear and distinct, and are only two in number, namely: (1) To reduce and keep down arterial tension; (2) to clear and keep clear the upper respiratory passages, so that the atmospheric pressure in the chest shall not be unduly reduced during inspiration.

[1] See *Medico-Chirurgical Transactions*, 1893, vol. lxxvi., p. 113

Now arterial tension may be reduced either by relaxing the arterioles or weakening the heart, and the iodides, morphine, calomel, or the salicylates relax the arterioles by clearing the blood of uric acid, while acids, and probably the inhalation of acid fumes act in the same way; on the other hand, tobacco, lobelia and other depressants probably affect the heart and the muscles.

Arterial tension may be kept down by reducing the amount of uric acid directly introduced or formed in the body, by altering the diet, and I have records of several cases where such alteration of diet has given great and permanent relief, and I have pointed out above that a diet containing an excess of animal food does harm.

Arterial tension may also be kept down by stimulating metabolism when this is possible; for as metabolism goes up urea and acidity rise, and the blood is kept clear of uric acid. (See chapter iv.) Now this may be done by regular graduated exercise, avoiding carefully the fatigue point, or by massage to improve the circulation and metabolism in the muscles and skin. Neither of these treatments, however, diminish the amount of uric acid in the body; on the contrary, they increase it, while they keep the blood clear, and when further stimulation of metabolism is no longer possible, as in old age, severe uricacidæmia is sure to supervene, bringing all its troublesome consequences with it. (See following chapter.)

For this reason I consider that diet which permanently reduces the amount of urate in the body is better treatment than stimulation of metabolism, which, while it clears the blood, causes urate to be stored in the body, or treatment by iodides or other drugs which produce the same result.

The condition of the upper respiratory passages is generally a matter for the surgeon; but, as I think, there is reason to believe that an excess of uric acid in the blood may by affecting their circulation tend to produce or keep up congestion of the nasal and other mucous membranes, I should be inclined, where such local troubles are slight and merely congestive, to give diet a careful trial before resorting to surgery.

CHAPTER X.

Dyspepsia and Gout of the Intestines.

As I have said, in the uric acid headache when the pain is severe, and mental and bodily exertion are almost impossible, when the skin and extremities are cold and the urine scanty, there seems to be good reason to believe that the circulation is equally defective in the glands and mucous membranes of the digestive system.

For the saliva is obviously scanty, and there are several well-known facts which render it extremely probable that gastro-intestinal digestion is almost completely at a standstill. The case I have mentioned in chapter vii. must, I think, go a long way towards proving that this is so in some epileptic fits; and it must surely be common experience with those who see much of migraine and similar "bilious attacks," that in one of these conditions food may be vomited, after several hours' sojourn in the stomach, in a totally undigested condition. I am suggesting that this is due to the defective circulation in the glands and mucous membranes concerned, produced by excess of uric acid in the blood.

Now it is clear that such defective circulation will account for the failure to digest and absorb either food or drugs, which characterises these conditions, and will further account for the putrefactive processes which, under these conditions, promptly take the place of digestion, they in their turn accounting for the changes in the urinary constituents noticed to take place in epilepsy by Drs. Herter and Smith (p. 138), possibly also for the somewhat similar evidences of intestinal putrefaction met with in some

conditions of anæmia (see chapter xii.), and as we shall see also in chapter xii., they may very probably account for the causation of oxaluria and its frequent association with dyspepsia and hæmoglobinuria.

The extremely fœtid motions which are often met with in dyspepsia, bilious attacks and diarrhœa are, I think, very often due to the cause of intestinal putrefaction just mentioned.

Then in chapter xii. I shall have to give notes of a case in which, along with these disturbances of circulation in the stomach and intestines, there was very distinct evidence of congestion and enlargement of the liver, these being associated in some attacks with a temporary albuminuria.

I mention this to show the possible effects of these circulatory disturbances on the liver, and we can already demonstrate their effects on the kidneys; further, to draw attention to the very close relationship in time between all these troubles, a relationship which I am endeavouring so show has its foundation in community of causation, and this very close relationship must be my excuse if in the chapters treating of these conditions I am driven to repeat to some extent what I have already said.

I must not forget, however, that my main point in this present chapter can be demonstrated by means of a very simple experiment. Let anyone swallow a few grains of salicylate of soda and watch how long it takes for the reaction with perchloride of iron to appear in his urine. Under normal conditions he may very probably find it in from 7 to 10 minutes. Let him then repeat the experiment some other day, when his arterial tension is above normal, when he has a headache, a bilious attack, or other form of gastric upset, and when his pulse is slow and his urine scanty, he will find that the reaction in the urine does not appear for a considerable time, possibly, as in the case of epilepsy mentioned before, not for hours. (See p. 138.)

But failure of gastric digestion and absorption is not only a result of uricacidæmia and the circulatory changes it produces, it is also a cause of further uricacidæmia, for the failure of digestion and absorption diminishes the blood's income of tissue, foods and acid-forming substances, and this, added to the deficient circulation in all the great metabolic tissues, tends ever towards a more and more feeble metabolism with lessening formation of urea, and of acids and acid salts, and an ever in-

creasing alkalinity of the blood and tissue fluids, which thus become ever better and better solvents of uric acid, and will take up more and more of it when it is available.

In this way, from uricacidæmia to dyspepsia, and from dyspepsia to uricacidæmia, we get a vicious circle which tends to extend itself and drag the patient down to ever lower and lower conditions of digestion and metabolism, and which must be completely broken through before any general improvement is possible.

Such is, I think, the causation of a very large number of dyspeptic troubles, an originating disturbance as indigestible food, irregular food, food taken in sequence to fatigue and exhaustion (see chapter viii.), sudden changes of diet, or weather, exposure to cold causing depression, one or all of these causes, or more frequently a mixture of them, upsets gastric digestion, which in turn increases the uricacidæmia, and the downward course begins, and if not promptly arrested, the patient becomes greatly reduced in strength and very anæmic (see chapter xii.), and then dyspeptic troubles become chronic, and for a time perhaps almost incurable. Then again, perhaps in the primary disturbance of gastric digestion putrefaction may supervene, and masses of food in this condition may act as irritants in the lower portions of the intestinal tract, and excite more or less local inflammation and diarrhœa.

In these conditions, as I have said, I believe that mercury and its salts act, not as local disinfectants within the intestinal mucous membranes, but by getting absorbed into the blood and clearing it of uric acid, with which they form insoluble compounds; digestion and absorption are thus once more allowed to proceed, because the capillary circulation throughout the intestines is restored, and putrefactive products soon cease to be formed.

All will, however, not be well in a moment; there may still be patches of gastro-intestinal irritation, due to the presence of the products of putrefaction and fermentation; and some diarrhœa may continue from this cause, and there will also remain some general lowering of nutrition and debility, and some anæmia, which will require special treatment in addition to keeping the blood clear of uric acid.

But supposing that before the process has been put a stop to some intestinal irritation has become considerable, passing in

some places even to slight inflammation, it is clear that when by mercury or other drugs we clear uric acid out of the blood we may very probably get a concentration of this substance in the tissue fluids round about such foci of irritation, and this will be still more liable to occur if, as the result of disturbed digestion there has been fermentation with excessive formation of acids, rendering the intestinal mucous membranes more acid than usual.

Such a concentration of urates in the fibrous walls of inflamed areas of intestine, just as they concentrate round the lowly alkaline fibrous tissues in joints, and in the liver, spleen and kidney, in several of which they may be present in quantities sufficient to be visible to the naked eye, constitutes what I have spoken of as gout of the intestines (*Practitioner*, vol. l., no. 1), and forms, I believe, the anatomical condition behind such conditions as colic, enteralgia, enteritis, and not a few cases of typhlitis.

And if there are present such foci of intestinal irritation, as the result of dyspepsia with putrefaction or fermentation of food substances, at the time when a dose of mercury drives uric acid out of the blood, it is little wonder that by still further concentrating the urates round the intestinal lesion it should greatly aggravate the trouble and produce severe gout of the intestines.

And we have also the evidence of Sir A. Garrod and others that urates may in this way produce severe inflammation of the intestinal walls, and may eventually be deposited there in such quantity as to form visible concretions.

Now Sir A. Garrod gives notes of the case of a very gouty man, aged 50, where, after exposure to cold, gout retroceded to the intestines, producing intense inflammation of the last eighteen inches of the ileum, as found after death. ("Gout and Rheumatic Gout," ed. iii., p. 439.)

And Sir Dyce Duckworth says: "Professor Hayem has recorded a case where enteritis occurred, the villi being strewn with small uratic encrustations;" and further on he says: "Severe colic, tympanitic distension, enteralgia, and diarrhœa, are sometimes distinctly referable to gouty disorder." ("A Treatise on Gout," p. 89.)

From these remarks it might very reasonably be supposed, that though the conditions mentioned do occasionally occur as the results of gout, they are somewhat rare, and therefore of little clinical importance.

My clinical and experimental experience has, however, led me to take a very different view, and to believe that a very large number of cases, such as I have mentioned, are neither more nor less than a gout of the walls of the intestinal tube, and that a knowledge of their true pathology places us at once in a position to effect a complete and satisfactory cure, by the use of the same drug, which in my hands, gives the best results in cases of arthritis, due to uric acid.

I shall further point out that such colic or enteritis can be produced by giving certain drugs, all of which have the same action on uric acid, viz., that of driving it out of the blood into the tissues.

Prominent among these drugs are the metals, mercury, lead, and zinc, all of them forming, as I have pointed out, insoluble compounds with uric acid, and I believe also that lead colic can be successfully treated by the same drug that is useful in gouty arthritis, and that lead colic is simply an enteralgia or enteritis, produced by the irritant effects of urate of lead in the intestinal walls.

I shall now have to point out that the same result can be produced by urate of mercury, urate of zinc, or even by urate of soda.

As in several other matters connected with gout, it was my own personal experience that first directed my attention to the points I am now bringing forward.

Some six or seven years ago, I noticed that when I was suffering from some gastro-intestinal trouble, such as that which commonly produces an attack of uric acid headache (migraine), and that when I treated this trouble by taking a small dose of calomel, I sometimes produced pretty severe intestinal pain, which was generally located in or about the right iliac fossa.

On one occasion, when a small dose of calomel (gr. i.) produced slight pain in this way, I thought that the purgative action had been insufficient and that a larger dose was indicated; the result of this, however, was to produce very severe pain indeed, which confined me to bed and the house for several days and made me quite unhappy about myself, as I feared that I had typhlitis.

At this time, however, I knew very little about gout of the intestines, and nothing at all about the solubilities of the urates

of mercury; hence beyond a mental note to avoid, as far as possible, the use of calomel for the future, the lesson was lost upon me.

A year or two later, when taking some cocaine for purposes of experiment, I was surprised to find that it was followed on several occasions by a somewhat similar pain; and this pain, partly due I think to cocaine, and partly the result of cold and occasionally wet feet late in the autumn, became chronic with relapses, and awakened my old fear of typhlitis and of serious disease.

So much was this the case, that I consulted a friend on the matter, and, at his suggestion, was making up my mind to take several months' rest and change of climate, when I chanced (still following out my experiments to some extent, or possibly prompted by some previous experiences) to take a few doses of salicylate of soda; and the effect was magical; the pain was better soon after the first dose, and in two days was gone for good and all.

I now began to see that I was not suffering from serious organic disease; but from a gout of the cæcum, accompanied by a certain amount of colic enteralgia and enteritis, and when I afterwards found out the insolubility of the urates of mercury, I was easily able to understand why this metal had produced the pain on a previous occasion and why salicylate of soda had cured it so completely on this last occasion.

Since this time I have had no further anxiety on the score of this intestinal disorder; I have often had it, and will undertake to produce it at any time, by the use of any of the drugs I shall mention presently; but I have now complete confidence that I can put an end to it in a few hours' time by means of salicylate of soda.

One of the first uses I made of the knowledge I had thus acquired, was to apply the same argument to lead colic; here is another metal whose urate is insoluble (Garrod). I have shown that, like mercury, it diminishes the excretion of uric acid and clears it out of the blood, and like mercury, it produces intestinal irritation and colic; if this is so, salicylate of soda ought to be useful in lead colic.

And in the one or two cases in which I have been able to give it this has certainly appeared to be so, and all symptoms cleared

up steadily and completely, the patients doing fully as well as under any other treatment with which I am acquainted. I have also treated several cases that were clinically typhlitis in the same way, and have every reason to be satisfied with the results.

One of the most recent of these was in the person of a relative of my own who is a member of the profession. I happened to hear that he was ill with what sounded like typhlitis, and I also heard that he had taken a dose of calomel shortly before the attack began. It at once struck me that this was a repetition of my own experiences, and I went to see him as soon as I could, told him what I had found out in my own case, and persuaded him to let me add a little salicylate of soda to the mixture he was taking.

The result was in every way as satisfactory as in my own case; he at once began to improve, and in two or three days was up and about, while prior to the administration of this drug it appeared only too probable that his illness would be a matter of weeks.

The history of this case is as follows. After one or two rather extensive dinners and champagne, he had a little digestive disturbance, and with the intention of putting this right he took a few grains of calomel, and a few hours later was seized with violent, colicky pain in the right iliac region. The pain came in attacks which were worse at night and caused nausea. There was an ill-defined fulness, with tenderness in the right iliac fossa, and temperature about 100° F. He asked a neighbour to come and see him, and lay in bed often groaning with pain, and with warm poultices constantly applied to the painful region; he took a mixture containing nepenthe and carminatives, and a nurse was obtained for him.

This was the condition of things when I went to see him, and with the concurrence of the neighbour who was looking after him, added salicylate of soda to the mixture, with the result mentioned.

There was, I think, no doubt in the minds of any of us that we were dealing with typhlitis, or a condition so like it that it deserved to be treated with great respect; but there was also in my mind no doubt from the history of its causation that it would yield at once to salicylate of soda, and this proved to be the case.

Among drugs with which I have from time to time produced somewhat similar intestinal troubles in myself are, in addition to lead and mercury, zinc which I have taken as the sulphate and as the phosphide, and Dr. Ringer mentions zinc colic ("Therapeutics," ed. xii., p. 254); and copper, of which the same author says (p. 252): "Copper salts taken for a considerable time in small quantities are said to give rise to a condition not unlike that produced by lead; for example, colic with alternating constipation and diarrhœa, and it is even said paralysis of the upper extremities, undistinguishable from that of lead." (See also a note on the effect of peas coloured with copper, in the *Lancet*, vol. i., 1892, p. 1445.)

I have, myself, had a patient under my care who worked in brass and had troubles resembling uric acid headache, which she attributed to her work; and what is described as brass-worker's ague has many points of resemblance to a severe attack of migraine. In these cases uric acid headache was no doubt due to an overflow of uric acid into the blood from that which had previously been locked up and retained in insoluble combination with copper. And we know that urate of copper is insoluble, as a process for estimating uric acid is founded on the fact. (Arthaud and Butte, *British Medical Journal*, i., 1890, p. 495.) The parallel, therefore, with lead and mercury is complete.

In addition I have mentioned the pain produced by cocaine, and cocaine also diminishes the excretion of uric acid, and acids, nux vomica and sulphates, especially sulphate of soda, occasionally act in the same way and cause some intestinal pain of a similar kind; and exposure to cold, or cold feet in winter, occasionally produce the same result, and all these factors have the same action on uric acid; they diminish its excretion in the urine, clear it out of the blood and drive it into the liver, spleen and fibrous tissues, especially into any fibrous tissues that have had their alkalinity diminished by any previous irritation or inflammation. They produce this effect on uric acid either by forming insoluble compounds with it, as in the case of the metals, or they diminish the solvent powers of the blood by diminishing its alkalinity, and under slightly different conditions any of them may produce gout of a joint, instead of gout of the intestines.

No one, I suppose, will deny that there is a large amount of

fibrous tissue in the walls of the intestines, and if the fibrous tissues in fascia, tendons and joints are liable to have urates deposited on them when they have had their alkalinity diminished by injury or irritation, I see no reason why the fibrous walls of the intestines should not be affected in exactly the same way.

Thus the case just quoted from Sir A. Garrod's book might have a causation somewhat as follows:

A gouty man has some more or less acute intestinal irritation (of dyspepsic origin) causing some nausea; this produces uric-acidæmia; on this there unfortunately follows exposure to cold, which raises the acidity and drives the urate out of the blood again, and, as in other cases a large amount of it goes into that piece of fibrous tissue which is most irritated and least alkaline, in this case the fibrous structure in the walls of the last eighteen inches of the ileum, this still further increases the irritation and acute gouty inflammation of this portion of intestine ensues, and becomes so serious as to cause death.

I have no doubt that if after death an extract had been made of this portion of the ileum it would have been found to contain far more urate than any other portion of the intestines of the same weight, and we see from the points mentioned by Sir Dyce Duckworth (previous quotation) that the gout may go on to deposit of urate visible to the eye.

Again we have some evidence pointing in the same direction in the part of the intestine commonly affected; why should the last eighteen inches of the ileum, or, in my experience, the cæcum and lower ileum be the parts affected?

I would suggest that the reaction of the intestinal contents has something to do with it; it is well known that those of the large intestine have an acid reaction, and it is not improbable that the alkalinity is diminished in the small intestines before the ileo-cæcal valves are reached.

Again, M. Bouchard ("Leçons sur les Auto-intoxications," p. 172), has shown that in certain dyspeptic conditions, especially in dilatation of the stomach, there is an excess of acid throughout the whole intestinal canal, and such acidity may cause local irritation, and thus form the starting point for a concentration of urates in the intestinal walls and an attack of gout.

Then any local irritation due to impacted fæces or foreign bodies may act in the same way, setting up a local inflammation

with fall of alkalinity, which is soon complicated by a concentration of urates on the irritated spot; in this way irritation in the vermiform appendix may precipitate a local attack of gout, which, as in other parts, the joints and the valves of the heart for instance, recurs and recurs till a more or less extensive lesion (perityphlitis) has been produced.

But it will be said if the reaction of the intestinal contents has anything to do with the gout attack and its localisation, then surely the stomach should be the place of all others in which these gout attacks should occur.

We all know the way in which the stomach is prevented from digesting itself by the free circulation of alkaline blood in its walls, but let there be local irritation, inflammation or stasis, then the acidity of the contents does affect the structure of its walls, and it does proceed to digest itself to a certain extent, and I can quite believe that such a local irritation may be kept up and made to recur by urate irritation; and not a few facts—which however, I shall discuss at some future time—seem to me to point to the probability of many attacks of gastralgia and gastritis being in reality gout of the fibrous tissues in the walls of the stomach. Sir Dyce Duckworth mentions the conditions found in one or two cases of gout of the stomach (prev. ref. p. 89).

I would suggest that those who in future are able to estimate the amount of lead in the organs and tissues of fatal cases of plumbism, should estimate at the same time the uric acid, to see whether they are present in their combining proportions, and therefore probably as urate of lead.

Professor Oliver in his interesting work on "Lead Poisoning" (p. 38) points out that during an attack of lead colic the pulse becomes hard, resistant and slow, and the urine becomes scanty and of high specific gravity; the action of urate of lead will explain every fact here mentioned.

While the lead is causing retention of uric acid (its first action) the pulse is quick and soft, the arterioles are relaxed, and the urinary water is profuse; but later on, urate of lead which carries uric acid out of the blood, and so relaxes the arterioles, is deposited in various organs and tissues, among others in the walls of the intestines; here it gives rise to pain and colic, and this quickly changes the whole condition, giving rise to the rebound or second action of lead.

The intestinal pain and colic produce nausea and failure of digestion and absorption. As a result of this, the acidity of the urine quickly falls, and the alkalinity of the blood rises, this dissolves out some of the urate stores and floods the blood with uric acid, which in turn causes the contracted arterioles, slow high tension pulse, and scanty urine.

Precisely the same series of events can be brought about by any drug or combination of drugs which have the same effect that lead has on the solubility of uric acid, and what I have called the rebound after mercury, opium, zinc, cocaine, or acids, and nux vomica reproduces all the phenomena that attend lead colic, as described by Professor Oliver.

But it will be said if the rising alkalinity dissolves out the urate of lead it ought to remove that which is irritating the walls of the intestine and put an end to the colic; and so it eventually does, and this is nature's mode of cure; but inasmuch as there is a considerable amount of local irritation and inflammation in the intestinal walls, the alkalinity of the fibrous tissues is lower here than anywhere else in the body, and this is the last place the rising alkalinity affects, and meanwhile the pain and inflammation go on.

But if at this time salicylate of soda is given, it acts as I have shown best in conditions of low alkalinity, and it dissolves out, and removes first of all the urates in the irritated intestine, because that is the place where the alkalinity is lowest; hence, as observed, it very quickly and completely relieves the colic, and it does this equally well whether it has to deal with urate of lead, urate of mercury, or urate of soda, and for the same reason that it is so useful in gout and rheumatism, because as I have pointed out, it is a solvent of uric acid. (*Med. Chir. Trans.*, vol. lxxi.)

But my experience in these matters has been shared by others, as I notice in Dr. Goodhart's work on "Diseases of Children," ed. ii., p. 545, a frequent stomach-ache is described as a "feature of the rheumatic child," and he also mentions that Dr. Marshall uses salicylate of lithia for this complaint, "he thinks with great advantage."

Speaking of stomach-ache reminds me that I have also myself seen several cases in which persons who had indulged in some excess of acid drinks in summer, got as a result a more or less

severe stomach-ache, and possibly some of these cases also are really gouty enteralgia, the acid acting in the same way as the drugs mentioned.

And again, Dr. G. A. Sutherland, writing "On some Symptoms associated with the Uric Acid Diathesis in Children" (*Brit. Med. Journ.*, vol. i., 1892, p. 856), mentions two cases of inflammation of the vermiform appendix, with marked tendency to recur, and even suggests that the calculi found in the vermiform appendix are composed of uric acid or oxalic acid.

I am indebted for the notes of the following interesting case to Dr. G. D. Logan, of Ecclefechan, the treatment, which he adopted with success, having been suggested by my writings on this subject.

"Called at 2 a.m., on March 15, 1893, to a case in the country, and asked to bring morphine with me. Found a woman, unmarried, about 24 years of age, suffering from severe abdominal pain and retching. Had arrived the previous day from Glasgow, where she had been for some weeks previously, more or less confined to bed with similar symptoms.

"Illness began in January, 1892, with a severe attack of diarrhœa which 'gradually turned into dysentery,' and though under constant treatment, she had never quite recovered from the looseness of the bowels and pain. In October of the same year she broke down completely, was sent to bed, and had a course of blisters and iodine on the abdomen, with morphine injections. As this gave no improvement she saw a consultant, who said that her womb and appendages were normal, that she was suffering from some neurosis, and advised a course of massage. This she had for a month; says she felt worse for it, and latterly could not bear the pain of rubbing.

"For the last three weeks the pain had been getting more severe, and she has vomited almost everything taken. She now requires two injections of morphine daily (gr. $\frac{1}{2}$ each), and can get no rest or sleep without them. She had for years been subject to severe, often recurring 'nervous headaches.' She had on one occasion been confined to bed for six months, as the result of a fall injuring her spine, but without any obvious lesions. She is not hysterical.

"On examination I could find nothing abnormal but the tenderness on pressure all over the lower part of the abdomen,

her hands were very shaky, and she was much run down in strength.

"I thought it would be a good test case for the treatment you advise, especially with the morphine habit she had developed. I stopped the morphine at once. I ordered fomentations with belladonna for the abdomen. Soup and milk for diet, and a mixture with soda salicylate, nux vomica and gentian.

"After the second night she was able to get sleep, though she missed the morphine greatly, but at the end of a week she did not miss it at all. She got six or seven hours' refreshing sleep every night, and the pain was much less.

"In ten days she was out of bed, and in three weeks she was able to go out walking. Had an excellent appetite, pain all gone, bowels quite regular, sleeping perfectly, and since then she has remained quite well."

This is an extremely interesting case, for it illustrates so completely many of the points I have mentioned.

First of all the "nervous headaches" which I should have very little doubt were due to uric acid, then the diarrhœa which became chronic, doubtless with considerable local irritation in the intestines. On the patches of local irritation urates were from time to time concentrated, and the treatment by morphine, which for a time cleared the blood of urates would favour their action in keeping up the intestinal irritation, hence she got steadily worse on the treatment; but as soon as a drug was given which removed uric acid from the body, in place of causing its storage in the tissues, the whole thing cleared up.

I must congratulate Dr. Logan on the thoughtful care which led him to apply my reasoning and suggestions to this case, and on the great success he obtained when others had failed.

Since I first wrote on this subject, I have seen and heard of quite a number of more or less similar intestinal or abdominal pains, which were promptly relieved by the administration of salicylates.

Diagnosis of the dyspepsia, which is due to uricacidæmia depends rather on the symptoms which accompany it, than on its own special characters, and where dyspepsia occurs in relation with high arterial tension, headache, fits, or mental depression, asthma, Raynaud's disease, paroxysmal hæmoglobinuria, or Bright's disease, or alternates with gout or rheumatism, as in

the case mentioned in chapter viii., there is a strong presumption that uricacidæmia is at least one of the factors in its causation and continuance. Then it will improve on drugs or diet that clear the blood of uric acid, and will be made worse by administration of urates. (See figs. 15 to 18.)

In the same way gout of the intestines is to be diagnosed from its relation to the taking of metals and drugs which, under other circumstances, might cause gout of a joint, as mercury, or lead; or the effects of cold, &c., in the cases mentioned.

The indication for treatment in the case of the dyspepsia is to keep the blood free from an excess of uric acid. In the case of gout of the intestine, it is to remove the urate from the irritated part as quickly as possible, by means of salicylate of soda.

CHAPTER XI.

Raynaud's Disease.

Just as we have seen in the previous chapter, that the defective circulation in the gastro-intestinal mucous membranes produced by uric acid, may account for many of the phenomena of dyspepsia, I think that there is good reason to believe that the defective circulation in the skin and extremities similarly produced, will account for the production of Raynaud's disease.

The defective circulation is indeed common to the whole body, but the skin and extremities are specially affected, because, as Raynaud points out, they are the parts of the body which are most exposed to loss of temperature, and the extremities again have a larger surface, in proportion to bulk, than any other part of the body.

It may be said then that Raynaud in his "Thesis," published in 1862, attributed the local asphyxia and symmetrical gangrene of the extremities which he described to a spasmodic contraction of capillary vessels.

He acknowledged that this might be a general condition, affecting the vessels all over the body at the same time, but producing serious effects only in the extremities, because these are the portions of the body which have most surface in proportion to bulk, and therefore most quickly lose their heat by conduction and radiation, and most early become cooled down below the point at which the life of the tissues can be continued ("Thesis," p. 166). He observed that at the time of an attack of asphyxia or gangrene of the extremities, the skin was everywhere cold and pale, and a case of which I shall presently give notes shows, I think, that the temperature of the body at a distance from the seat of attack falls at the time of an attack, and rises again as it passes off.

I shall also point out that there is good reason to believe that the vessels of the kidney are contracted at the same time with those of the skin, and Raynaud himself mentions the signs of this without understanding their import; and there is also some reason to believe that the vessels in the brain, lungs, and other viscera are in a similar condition.

Raynaud himself, however, gives no good or satisfactory reason why the arterioles and capillaries should be affected by this spasmodic contraction: it is true, he remarks, that it is often met with in nervous people, and those who suffer from hysteria, epilepsy, &c.; but what influence he attributes to the nervous system in producing these phenomena all over the body is not very clear.

At this point I think that my researches come in, and I have suggested that the vessels are contracted owing to the presence of uric acid in the circulation (*British Medical Journal*, February, 1889, p. 291).

I will now give notes of some cases, and will then discuss Raynaud's cases and argument.

Margaret C., aged 3 years, came among my out-patients September 23, 1889. Her mother said that some of the toes of both feet were cold and blue, and child complained of pain in them. The right foot was seen to be blue-black, cold, and tender, as far as the middle of the metatarsal bones, the left foot had the second, third, and fourth toes blue-black and cold, and the colour extended in lines a little into the sole of the foot. Second sound of heart relatively loud. Pulse irregular and marked plus tension. Had measles twelve months ago, and pertussis the same time. Has not had any fever lately. Has three sisters who are all well.

Father subject to gout, his family also subject to it and to phthisis. Mother well.

The feet were wrapped in wool and a quarter of a tabella of nitro-glycerine given frequently, and she was admitted.

Sept. 24.—Much better. Feet are hot and a little tender, but the colour and coldness have both gone. Pulse 120; heart, first sound rather weak, second sound relatively loud. Urine of the attack yesterday gives a uric acid urea relation 1 to 8.3. An enormous excess of uric acid, but there is no albuminuria. Given a little dilute nitro-hydrochloric acid and ♏i. of tinct. opii. twice a day.

September 26.—Going on well; urine of this day gives a relation, uric acid to urea 1—20.7.

September 27.—Had another attack in the evening, the left foot being most affected this time; it was blue as far as the ankle. In the right foot only two or three toes were blue, just the reverse of the previous attack. Was again given nitro-glycerine. Urine of the attack (probably a mixture) gave uric acid urea relation 1 to 22. Urine later on, after all the nitro-glycerine had been given, 1 to 53. The first lot of urine was a considerable quantity, 450cc., and probably included urine before as well as during the attack, hence the relatively small amount of uric acid —1 to 22—as compared to 1 to 8 in first attack. The great effect of nitro-glycerine on the excretion is well shown in the excretion 1 to 53, which is in marked contrast with 1 to 22.

September 28.—Nearly all right again, and only a few scattered petechiæ and some œdema marked the parts of the feet affected yesterday.

It was now noticed that there was some peeling on the hands and chest, and, thinking that she might have had scarlet fever, she was sent out.

Her mother denied that she had had any rash or sore throat previous to admission, and I saw her a few days later at her own home, and examined her sister, who showed no signs of peeling.

Eliza H., aged 6. Admitted under my care in the Royal Hospital for Children and Women, November 27, 1890.

Her family have always lived in London. There are three brothers and sisters younger and one older than the patient. Mother has had nine children born alive, no miscarriages.

Mother is subject to cough.

Mother's mother and mother's brother had rheumatic fever.

Father's mother had "chalk gout."

No ague in family.

Patient had measles and bronchitis when 15 months old, and whooping cough at 4 years old.

Eyelids and face generally very pale and puffy. Has conjunctivitis and opacity of corneæ.

On admission—pulse 120, temperature 100°, respiration 24.

Soon after admission, she passed some urine which was almost black, threw down a grumous deposit, and contained a large amount of albumen. A few hours later it was the colour of dark sherry, and later still, quite normal.

December 1.—Urine to-day amber clear, acid, 1018. Phosphates. No albumen. I examined her heart and found reduplication of the first sound between the apex and the left border of the sternum, and a loud second sound both at apex and base.

Pulse quick, 80 to 105, irregular in force and time; and it was difficult to judge by the finger as to the tension, but pulse traces showed at times considerable tension. When the pulse was quick, I think probably there was some failure of the heart, and tension was not well maintained on this account.

Spleen dulness normal.

The urine of November 28 was port wine-coloured, with a grumous sediment, 1018. Contained a very large amount of albumen (about 10 or 12 parts per 1,000, Esbach). Gave hæmoglobin lines with the spectroscope, and a relation of uric acid to urea of 1 to 30.

December 2.—"The child's hands were washed with cold water at 6 a.m. After this she was well till 1 p.m., when she began to complain of pain in the hands, which were seen to be quite blue up to the level of the wrist. This blueness persisted up to 1.10 p.m., when the colour only remained beneath the finger-nails; the rest of the hands were red, puffy, and markedly swollen, but quite cold; the puffiness and redness gradually faded, and at 2.30 p.m. the hands were normal in appearance and temperature. Pulse 80, no marked plus tension during the stage of blueness and congestion. Heart first sound prolonged, second sound accentuated at apex and base. The child had marked pallor, and appeared to have intense headache during the attack in the hands, but said she did not know what was the matter, and had no headache. At 2.30 p.m. she sat up and began to play with her toys.

"Blood drawn from finger as congestion stage was passing off showed marked excess of white cells, which were actively motile and putting out many processes. Red corpuscles formed bad rouleaux, and scattered among them were collections of bright refracting nuclei about the size of one-sixth of a red cell, and it appeared as if in places the cells had burst and discharged their contents." I am indebted for the above description of an attack and the condition of the blood to the notes of my colleague, Dr. S. W. Wheaton, who was then Registrar.

December 4.—Urine of twenty-four hours, ending this morn.

ing, during which there was no attack, was 19 ozs., amber smoky, turbid, 1020, faintly acid. No albumen, some phosphates, uric acid, urea relation 1—17.

Had attacks of local asphyxia in hands or feet, or both, on December 6, 7, 8, 9. On the 11th and 12th there were no attacks, in spite of her hands being washed in cold water as before. The above attacks lasted from ten to forty minutes, and attention was directed to them by the child complaning of pain in the affected members. They were not accompanied by any marked rise of temperature, or followed by hæmoglobinuria, in fact, the temperature was sub-normal all the time.

December 13.—Urine of twenty-four hours, ending 8 a.m. to-day, 24 ozs., pale amber, turbid, neutral, 1016. Urea, 1.2 per cent.; uric acid, 0.04704 per cent. Relation, 1 to 25. Weight, 38 lbs. Urea, 3.5 grains per pound, which, for a child of her age, is very low, and shows failure of nutrition.

Had a slight attack in the right hand at 7.15 this morning, lasting ten minutes.

December 15.—Urine of twenty-four hours, 25 ozs., pale amber, slightly acid, 1019. Urea, 1.4 per cent.; uric acid, 0.05712 per cent. Relation 1—25.

Urea still very low. She is on farinaceous diet, and sister says she is always very hungry (had she been starved?). I ordered her to have meat and be fed up.[1] No doubt this low nutrition and relative excess of uric acid is the cause of all her trouble.

December 16.—Had four distinct attacks in hands and feet, first at 11.25 a.m., second, 4.25 p.m.; third, 4.50 p.m.; and fourth, 5.30 p.m. Urine passed between 9 and 11 a.m. to-day, 2½ ozs., amber, turbid, neutral, 1025. Uric acid urea relation, 1—19.

Urine 11 a.m. to 1 p.m. (being a mixture of the urine corresponding to the attack at 11.25 a.m., lasting twenty minutes, with the urine of the remaining one hour and forty minutes free from attack), 1026, faintly acid; uric acid to urea, 1 to 23.

There was thus apparently less uric acid at the time of the

[1] I did not at this time know that meat directly introduced uric acid into the body, (see p. 66), or I should not have ordered it, and no doubt this partly accounted for the continued excess of this substance in the urine.

attack than before it, but as I have pointed out in the case of headache, epilepsy, and other paroxysmal effects of uric acid, there is a variation in the excretion in both directions, a plus excretion during the attack, and a minus before or after it, or both, and when the separation is not accurate, as in slight attacks it can very rarely be, the minus excretion before or after the attack more than balances the plus excretion during the attack (which only lasted twenty minutes out of two hours' urine), and we get the result here shown, namely, that there was a greater excretion in the two hours before the attack than in the two hours including the attack; in both periods, however, there was a considerable excess of uric acid, and the urine is, after all, but an imperfect index of the amount of uric acid in the blood. (See pp. 49-50.)

December 19.—Had no attack on the 17th and 18th. To-day she had an attack at 1.50, lasting only ten minutes, but followed by a rise of temperature to 102.8°, and the urine passed next after this at 5 p.m., contained hæmoglobin.

Urine passed at 1 p.m., before the attack, pale amber, slightly acid, 1026; uric acid to urea 1—21.

Urine passed at 5 p.m. (the first after the attack), grumous, red-brown, with powdery sediment, strongly acid, 1030. Hæmoglobin lines. Much albumen, but part of the turbidity clears with heat (? urates). Uric acid urea relation, 1—22. Total urea in 100 cc. was 49 grs. Total uric acid, 2.2 grs. Total acidity reckoned as oxalic acid, 5.8 grs. Relation of acidity to urea, 1 to 8.4, that is to say, acidity was low, and with a low acidity we had a large excretion of uric acid, 1—22. But I said above, the urine was strongly acid; how then, it may be asked, was the acidity low? I reply that the urine (as is generally the case with excess of uric acid in the blood) was a very concentrated one, and the excretion of water small; hence the apparent acidity was high; but when we came to reckon the total acidity by the side of the total urea we find that the acidity is relatively low, for we only find 1 grain of oxalic acid for 8.4 grains of urea, whereas my researches show that taken over a long period of time, the relation of acidity to urea is 1 to 6.1; 1 grain of oxalic acid for every 6.1 grains of urea, whereas here we only got 1 grain for 8.4 grains of urea, so that, as I said, acidity

is really low, though, estimated only with a piece of litmus paper it would appear high. Such is the difference between exact and inexact investigation, a difference, I regret to say, not always appreciated.

What really happened in the attack of hæmoglobinuria was, I have no doubt, somewhat as follows :—At the time of the local asphyxia, 1.50 p.m., there was intense uricacidæmia, and an enormous excretion of uric acid in the urine, having the relation, say, 1—8 or 1—12, but in this case the attack only lasted for ten minutes, and the excessive excretion only went on probably for half an hour, but we unfortunately got no urine passed till 5 p.m., nearly three hours later. Meanwhile the temperature has risen, the alkalinity of the blood has diminished, the excretion of uric acid has fallen greatly, possibly down to 1—40 or 1—50, showing that there is no longer any excess of it in the blood, and the acidity of the urine has risen (it was possibly alkaline at the time of the attack), but the blood has been flooded with hæmoglobin, and this slowly finds its way out by the kidney. The result is that in the urine passed at 5 p.m. we have plenty of hæmoglobin, a low acidity, a large excretion of uric acid, 1—22, though this, in all probability, was the product of a mixture of the very much larger excretion during the attack with the very much smaller in the 2½ hours that followed it, so that the relation of uric acid is reduced from 1—8 to 1—22 ; just as the acidity is a mixture of the alkaline urine of the attack with the highly acid urine of the 2½ hours following it, when with high temperature there would certainly be a rise of urinary acidity, and a corresponding fall in the alkalinity of the blood.

Now that I have gone into these matters at length, I shall not require to repeat the explanation of the same phenomena in subsequent attacks.

Dr. Wheaton examined the blood one hour before an attack, and found 3,800,000 red cells per cubic millimeter; he again examined it one hour after an attack during hæmoglobinuria and found 2,990,000 cells only, a very great diminution. He repeated the examination on two subsequent occasions with similar results; and also found that the blood after the attack showed increase of white cells, and increase of coagulability.

December 20.—She had an attack of local asphyxia in both feet, lasting from 6.55 to 7.30 and followed by a rise of temperature to 99.8°. The urine passed after this, at 8 p.m., contained hæmoglobin.

Some urine passed before (? how long) the attack gave a relation of uric acid to urea 1 to 28, and that passed at 8 p.m. containing hæmoglobin, gave a relation 1 to 30. Here, again, I have no doubt there was an admixture of the excretion of before or after with that of during the attack, but as I was unable to obtain definite information as to the hour at which the specimen before the attack was passed, no valid conclusion can be drawn from my results. I got many such results with the uric acid headache before I found out the importance of separating carefully the urine of the attack.

December 23.—Local asphyxia toes of both feet 3.20 to 3.35 p.m., or lasting slightly till 4 p.m. Urine passed during the attack of a pale port-wine colour (a mixture of before and during), slightly turbid, alkaline, 1022; uric acid to urea 1 to 23.

Urine drawn by catheter at 4 p.m. (the end of the attack, excretion of about half an hour) dark port-wine colour, brownish deposit, slightly acid; uric acid to urea 1 to 28.

The remarks I made before about the effects of admixture apply here.

On December 21 she passed some hæmoglobin at 6.15 p.m., again on the 24th at 1 p.m., and on the 25th at 9.30 a.m.; in none of these cases was the passage of the hæmoglobin apparently preceded by local asphyxia; possibly the attack escaped observation; the child was very heavy and dull in the attacks, and if other children were making a noise, her first cry of pain might not have been heard. Later, on December 25, however, 5.15 p.m., both feet were affected, and remained so for about an hour, and the urine passed at 6 p.m. contained hæmoglobin, as also the specimen next passed at 6.15 a.m. on the 26th, but that at 9 a.m. on the 26th was clear.

December 28.—She had an attack in which the left foot led the way, and was followed by the right from 5.15 to 7.30 p.m.

December 29.—The hands and feet were both affected from 5 p.m. to 6 p.m., and the temperature rose to 100.8°, but the attack was not followed by hæmoglobinuria.

December 30.—The feet and hands were affected from 3 to 3.45 p.m., and again from 5 to 8.30 p.m. The urine passed at 8.30 p.m. contained hæmoglobin, and that at 9.30 the same.

I did not estimate the uric acid urea relations in any of these specimens, because it did not appear to me that the separation

was sufficiently accurate to make it worth while to do so; the attacks were slight, lasting from only a few minutes to half an hour, and in no single instance was the urine corresponding to the attack obtained separately.

In the previous more severe case of Raynaud's disease, where an attack lasted nearly twenty-four hours, there was much less difficulty about obtaining the excretions corresponding to the attack, and I got, as I have said, a relation of 1 to 8. That is to say, with the more severe and prolonged attack there was a greater and more continuous excess of uric acid in the blood and urine.

December 31.—Hands and feet affected from 5.15 to 7.30 p.m.

1891. January 4.—Left hand affected from 3.25 to 4.10 p.m.

January 5.—Hands and feet affected from 9.30 to 10.45 p.m.
Right hand affected from 1.5 to 1.30 p.m.

,, 6.—Hands affected from 1.30 to 2.30 p.m., and temperature rose to 99.4°.

,, 7.—Hands affected from 9.50 to 10.10 p.m.
Right hand affected from 5.10 to 5.35 p.m.
Both feet ,, ,, 6.45 ,, 7.15 ,,

,, 9. ,, ,, ,, 6.45 ,, 7.45 ,,

,, 14.—Both hands ,, ,, 6.5 ,, 6.25 ,,

,, 15.—I examined the urine of twenty-four hours ending 2 p.m. to-day, 18 oz.; sp. gr. 1018, and found:—Urea, 1.7 per cent.; uric acid, 0.06384 per cent.; total urea, 161 grs.; uric acid, 5.2 grs.; acidity, 15.7 grs.; uric acid to urea, 1 to 27; acidity to urea, 1 to 9. This shows that urea is still very low per pound of body weight for a child, acidity is low, and uric acid high; hence recurrent excess of uric acid in the blood, which is the cause of all our trouble.

She is up and going about, but seems dull and cross. Eyes still very bad.

January 17.—Feet affected from 12.5 to 12.45 p.m.

,, 18.—Both hands affected from 10.30 to 11.15 a.m.
Left hand affected from 5.30 to 6.30 p,m.

,, 19.—Feet and hands affected from 5.45 to 6.30 a.m.
Right hand affected from 5.10 to 6 p.m.

,, 20. ,, ,, ,, 6 to 7.15 a.m.
,, ,, ,, 11 to 11.30 a.m.

,, 22.—Left hand affected from 5.40 to 6.15 p.m.

On this day, as the attacks seemed to be pretty frequent, I determined to treat the uric acid, and she was accordingly put on salicylate of soda, gr. viij. three times a day after meals, and had the first dose on the evening of January 22, after the forty-second attack of asphyxia. She was also given a small dose of acid and strychnine three times a day to aid the action of the salicylate.

From this she went for twenty days right off without any attack whatever, her forty-third attack of local asphyxia occurring at 2 p.m. on February 11, while out on the roof of the hospital.

January 29.—Better and more cheerful, and all the nurses bear witness to the improvement in her temper, though her eyes are still very bad.

February 5.—Still no attack, and temper continues to improve. Yesterday, however, the temperature rose to 101.8° at 10 p.m., but there was no sign of an attack in limbs or urine.

February 11.—Attack while on roof at 2 p.m., part affected not stated.

February 13.—Feet and hands affected 11 a.m. to 1.30 p.m.; was out on the roof early in the morning.

February 14.—Seems well in herself, and is singing away; Salicylate mixture to be given four times a day.

February 19.—No attacks; has been on the roof twice for about an hour each time. Going on well.

February 22.—She had her forty-fifth and last attack in both ears from 7 to 8.30 a.m., and it is noted that her temper was very bad at the time of the attack.

February 23.—Temper is much better now than before salicylate was begun.

March 5.—Still no attacks in spite of exposure on the roof in the cold of the morning at 7 a.m. All drugs left off to-day.

She was on the roof on February 17, 18, 25, and 27 without any effect being produced.

March 9.—Weather very cold with a strong east wind, so salicylate was resumed again.

March 12.—Was on the roof at 7 a.m. to-day. Thermometer 27° F. No effect.

She now went on quite well, her temper keeping placid, and she seemed bright and happy in spite of the condition of the eyes,

which remain so bad that she can only see very indistinctly, and is afraid to walk or run by herself.

May 7.—Well in herself now, but had an attack of tonsillitis about two weeks ago, for which, as another child in the ward had diphtheria, she was isolated; she, however, got quite well, and had no sequelæ.

About a week ago I put her on small doses of liq. calcis chlor. with the view of trying whether I could produce some retention, of uric acid, and then, by bringing it out into the blood again, produce an attack. I, therefore, examined the urine of twenty-four hours ending this morning, and found total urea 187 grs., uric acid 7 grs. Relation 1 to 26. Acidity was still low, but urea had risen somewhat in accordance with the improvement in the child's general condition, being now about 4.6 grs. to the pound. It seemed, however, that with this continued low acidity I was not likely to produce much retention of uric acid, and I therefore gave up the attempt, and sent the child home.

June 22.—She still attends as an out-patient; is cheerful and well, getting fat, and has had no attack of any sort.

She had thus altogether 45 attacks of local asphyxia and 9 of hæmoglobinuria; 42 out of the 45 attacks occurred in 52 days from December 2, 1890, to January 22, 1891, and 3 attacks in 31 days, from January 23 to February 22, 1891. In the week ending January 22, the day on which salicylates were begun, she had 8 attacks, and then she went, as I have said, 20 days without an attack at all; then came 3 attacks in the next 11 days, and after that none, in spite of cold weather (as our winter certainly did not end on February 22) and exposure on the roof as before.

The points of greatest interest to me are the pallor and headache which occurred during an attack, as described by Dr. Wheaton. The fact that her temper was generally bad, and was worse in the attacks; also that it improved when salicylates were given, to such a marked extent as to be noticed by all who saw her.

The case also illustrates fairly well the fact observed by others, that the attacks are generally in the morning; and this corresponds with the well-known fact, that the greatest excretion of uric acid in the urine, and probably the greatest uricacidæmia, occurs in the alkaline tide of the morning.

Dr. Wheaton says that the pulse during an attack was 80, and showed no marked plus tension.

But 80 is a somewhat slow pulse for a child of 6 years. The quickest pulse on her charts is 142, and the slowest 54, and pulses of 60, 64, and 72 on several occasions corresponded with attacks, and these show considerable bradycardia, which, as I have argued, is due to uricacidæmia. (See page 106.)

As to tension, I found that it was very difficult to estimate by the finger in this case; but some traces I obtained, show considerable tension though the pulse rate was above 80. (See *Transactions of the Medical Society*, vol. 15, p. 155.)

Again, I think that when her pulse was quick it was not always because the tension was low, for there were several signs of heart failure here, and, as I know from observations on other cases, when the heart fails before high tension its systoles become imperfect (as some of my traces from this case show) and its action quick; and Marey's law that pulse rate is inversely as arterial tension, or that the length of the ventricular systole is directly proportional to the amount of arterial resistance, holds only so long as the heart is equal to its work; and when the systoles become imperfect and the heart quickens, tension is not maintained well in spite of great peripheral resistance and contraction of arterioles. "A long pulse means a labouring heart,"[1] but a short pulse with peripheral resistance means a failing and dilating heart.

Hannah E., age 47, admitted into the Metropolitan Hospital, April 7, 1892.

Had one child, which died at the age of five months, of "pulmonary consumption."

Has two sisters, who are well.

Had five brothers, but one is dead, and one dying of consumption; three are well.

Father died of apoplexy.

Mother, aged 66, is well.

Patient had rheumatic fever twelve years ago; phlebitis of right leg ten years ago; inflammation of lungs eight years ago; bronchitis twice since that.

Fingers have been painful and blue, with tendency to ulceration on and off for three years.

[1] Mahomed, *Guy's Hospital Reports*, 1879.

The right hand was first affected, and the left became affected in December, 1891, when she was ill with bronchitis.

The first symptom was pallor or blueness of one or more fingers, especially after washing the hands in cold water. Later on, blebs formed on the fingers and burst.

Fingers are growing shorter and more stumpy, and are getting more painful.

Has general shivering when the attacks of coldness come on in the fingers.

A pale, poorly-nourished woman.

Temperature generally subnormal; pulse 80, irregular in force.

Heart.—Apex-beat in fifth space, just outside the left nipple-line. Blowing systolic murmur at the apex. Other sounds, nothing remarkable.

Lungs.—A few mucous râles both sides; no dulness.

Abdomen.—Nothing abnormal. Bowels tend to be constipated.

Urine.—Specific gravity, 1012; contains a trace of albumen. Thinks she has been passing more water of late.

Legs show dilated venous capillaries.

Right hand.—All fingers somewhat blue and shining, but the first and middle finger have a red tinge, and are somewhat clubbed, while the ring and little finger are tapering, and somewhat colder than the others.

Nails on the first and middle finger are short and have transverse striæ, the others have longitudinal striæ.

All fingers are marked with scars, which have dried up, and all are more or less painful.

Left hand.—All fingers are blue and shine, and taper from the first interphalangeal joint to the tip. All are abnormally cold and rather tender.

On the index finger there is an excoriation just in front of the nail, where a slough has separated.

The middle finger has a suppurating point under the nail, and on the last phalanx there is a bleb the size of a filbert, containing dark fluid and a slough, very painful.

The ring and little finger are tapering and cold.

All nails are curved and longitudinally striated.

Sensation is fairly perfect in all fingers.

The urine was examined on several occasions, and it always contained a trace of albumen, and had a low specific gravity.

I came to the conclusion that we were dealing with chronic Bright's disease and chronic bronchitis, dilatation and hypertrophy of the left ventricle, with or without some lesion (rheumatic) of the mitral valve, with, at the present time, some failure of compensation, shown by the irregular force of the systoles, and the somewhat rapid rate of action; and that with these conditions it was not very extraordinary that we should find what we may call chronic Raynaud's disease, with exacerbations affecting the hands.

April 7.—I put the patient on nitro-hydrochloric acid and nux vomica three times a day before meals, and salicylate of soda three times a day after meals, and ordered that a tablet of nitro-glycerine P.B. should be given from time to time when the fingers were more than usually painful.

April 12.—Still has attacks of pain in the fingers, which turn white and blue, and get very cold. The pain in them wakes her up. Takes the nitro-glycerine tabloids, and is sure they do good; feels warmth and comfort returning to fingers about three-quarters of an hour after one.

April 13.—Pains are relieved by the nitro-glycerine. Temperature to be taken before and after a tabloid.

April 14.—Complains of coldness of left foot, the great, second, and third toes, being painful and rather blue.

April 16.—Temperature in axilla .6° up after a tabloid had relieved the pains. Observation to be repeated.

April 19.—Better; no attacks at all. No tabloids taken; fingers are less cold.

April 20.—Had an attack with a headache at 7.30 a.m. to-day. A tabloid was given at 8 a.m., and a second soon after. Got quickly better after the second tabloid. Temperature in the axilla at the time of the attack was 97.2°; when the tabloids had relieved the fingers it was 97.8°, and it rose to 98.2° in the evening.

April 27.—No attacks for several days; the slough on second finger of left hand has separated and the ulcer is healing.

May 3.—Has a headache to-day, and the fingers are colder; they were fairly warm yesterday.

May 4.—Above mixtures left off, and phosphate of soda ʒss. given three times a day in their place.

May 7.—Has an occasional headache, but the fingers are only slightly affected; no severe attacks of late.

May 9.—Had a bad headache at 11 a.m. to-day.

May 11.—Fingers very blue and cold to-day in spite of the warm weather.

May 14.—Fingers are much less blue to-day.

May 17.—Had a bad headache at 2 a.m., and the fingers are worse to-day. The index finger of the right hand is getting swollen and painful in the last phalanx. After this she soon got better, and went out.

The temperature was generally subnormal, the highest being 99.2° on the evenings of April 20 and 27, and the lowest 96.6° on the morning of April 8.

Of Raynaud's twenty-five cases, twenty were women; they were for the most part young, only one being (48) older than this patient.

One of his cases, No. 18 had mitral disease (constriction). This patient was worse in the spring of the year, and Raynaud mentions the autumn and spring as being the common seasons of onset.

This case also fulfils Raynaud's definition in that the troubles were to a large extent symmetrical; and like it, also, several of his cases became chronic, lasting for years, with periods of intermission—a condition of things which he thinks is specially seen among the slighter forms of the trouble.

In the patient whose case I have just narrated above, I did not estimate the uric acid for two reasons: first, because, as I have said, her attacks were not very well marked, so that it would have been difficult to separate the urine corresponding to them; and second, because I came to the conclusion that she had Bright's disease, and there seems to be reason to believe that Bright's disease, especially in its acute stages, inteferes with the elimination of uric acid, so that there may be an excess of uric acid in the blood, without any corresponding excess in the urine.

Eliza H. had hæmoglobinuria with some of her attacks, and I shall give presently the amounts of uric acid I found in the urine in other cases of hæmoglobinuria. This patient also had pallor of skin, headache, and bad temper at the time of her attacks; and when she was put on drugs similar to those I gave to Hannah E., all her symptoms greatly diminished in severity or disappeared.

In the case of Hannah E., the family history is of some interest, for her father died of apoplexy, for which we may not be far wrong in reading chronic high arterial tension, Bright's disease, and cerebral hæmorrhage; then two brothers had phthisis, and there is almost certainly an important connection between gout and phthisis, and one of the links of this connection stands out, I think, pretty clearly in the fact that the substances (uric acid, &c.) which contract the arterioles and capillaries of the general circulation contract also those of the lungs and diminish the output of water from them. (See p. 182.)

She herself had rheumatic fever, which as I have endeavoured to show, is due to uric acid, and two years later phlebitis in the leg, the relationship of which to gout is well known.

Then the troubles for which she was admitted became worse in the spring, and I have shown that in spring and summer there is a plus excretion of uric acid in the urine, the sign that an excess of it is passing through the circulation on its way to the kidney, while in the winter there is a diminished excretion with some storage of urate in the organs and tissues, the plus excretion of the warm season being the result of, and to same extent proportional to, the minus excretion of the cold. (See p. 15.)

Then her attacks were often in the morning—in fact, just at the hours when in the normal physiological cycle the excretion of urate and the amount passing through the blood is greatest, and we have all the signs of its excess in the blood in the cold and pale surface, and the headaches which so frequently accompanied the attacks, and much the same may be said of the majority of the attacks in the case of Eliza H.

There are a few points also which I should like to draw attention to in Dr. Southey's very interesting case of symmetrical gangrene, which I was fortunate enough to see, and which is recorded in the *Transactions of the Pathological Society*, 1883, p. 286.

The patient was a girl under three years of age. It is recorded that her face and the rest of her skin presented an ashen pallor—"axilla temperature 99.4°, pulse 120, small, and a little wiry at the wrist." (She was evidently passing into the stage of reaction with rise of temperature.) Her urine was alkaline, deposited urates and phosphates, and contained albumen. There could, I think, be no doubt that this alkaline urine contained an excess of

uric acid relative to urea, and that the albumen was probably due to blood changes similar to those that produce hæmoglobinuria.

At the *post-mortem*, which is interesting as adding one more to the rather scanty records of such observations (Raynaud records only three), nothing abnormal was found in the vessels of the asphyxiated parts, but the blood was everywhere fluid and "like black cherry juice."

In the discoloured parts the skin and connective tissue were chiefly affected, the muscles were only a little stained, and there was no effusion into the joints; and this is interesting, as Raynaud remarks that the lesions are more superficial than one might at first sight expect.

From the parents it was made out that there was undoubted syphilis in the father's family, and he had suffered from hæmatemesis.

The child had an attack of "febrile purpura" in October, and a feverish attack for three days from November 13 to 16.

Her last illness began on the evening of December 1 with headache. Next morning she was apparently well, but at 4.30 p.m. complained of her legs, and her father seeing bruises on them, rubbed them, which appeared to make the pain much worse, and from that time the trouble increased up to her death.

I think it quite possible that the final attack was a post-febrile rebound coming after and due to the fever of November 13 to 16, similar to the post-febrile conditions we see every day after pneumonia, typhoid, scarlet, and other fevers, with its symptoms of slow, high-tension pulse (post-febrile bradycardia), subnormal temperature, and general depression, and which are due, as I have shewn, to the urate which is stored during the fever passing through the blood, when, with falling temperature and falling acidity, the conditions become favourable to its solution and excretion: in a word, there is post-febrile uricacid-æmia and its symptoms, and Raynaud's disease is, I believe, a mere exaggeration of some of these. (See pp. 109 and 154.)

In the case of my patient Margaret C., the attack bore precisely the same relation to a previous fever, probably scarlet fever.

It may be objected that in Dr. Southey's patient the interval from November 16 to December 1 was too long to allow of this

explanation, but I think it is very probable that the fever did not really come to an end quite as soon as the parents made out, and the way in which serious diseases are allowed to pass almost unnoticed among the children of the poor is familiar to us all. The first sign of this post-febrile uricacidæmia was the headache of December 1; possibly this was followed by a little febrile movement which temporarily raised the acidity and made her appear bright and well next morning, but by the afternoon this had come to an end, and at 4.30 p.m., which comes in what I have spoken of as the afternoon alkaline tide, the full force of the uric acid storm, no doubt reinforced by the temporary fluctuation of the previous night, affected her vessels, and the gangrene began.

A glance at the plate which accompanies the description of Dr. Southey's case shows that the asphyxia affected first and chiefly those parts of the legs which in children of this age are commonly left without covering, and so are exposed to great loss of heat by radiation and conduction; so that Raynaud's argument (given above) with regard to the hands and feet will hold also in this case, for it was the skin, and not the deeper tissues that were affected.

The most interesting part of Raynaud's thesis is that in which he discusses the etiology of the trouble, and sums up the arguments for and against each theory. He devotes a good deal of attention to arteritis, but sums up against it on the grounds that there is no anatomical proof of its presence, and that permanent changes in the vessels will not account for alterations in circulation which are paroxysmal and temporary.

Much the same conclusion is arrived at with regard to the nervous system, though he is himself more in favour of this explanation; but he points out that though a lesion of nerve structure undoubtedly influences the nutrition and sensation of the parts supplied by the injured nerve, the effect is local, and does not affect especially the circulation, while the condition he is describing affects primarily the circulation, the altered nutrition being secondary to this, and it is not entirely local, as the whole surface of the body is affected to some extent in the same way; and he finally concludes that spasmodic contraction of capillary vessels gives the best explanation, for the following reasons. The circulation in the arteries is little if at all affected in the paroxysms; the large veins are also free, and obstruction of a vein gives rise to totally different conditions from those met with in the cases he is

describing. The chief point in local asphyxia is the extreme slowness with which the venous capillaries refill when emptied by pressure. In an asphyxiated finger, if the capillaries be emptied by pressure, as much as thirty seconds may elapse before they regain their colour; in a normal finger the blood will return in one or two seconds. If a ligature is passed round a finger so as to obstruct the veins, it becomes purple and congested, it is true; but if a pale spot is produced by pressure, the blood returns into its vessels even more quickly than in the normal condition. It is evident, therefore, that the obstruction is neither in the arteries nor in the veins, but in the small vessels that lie between them, and the obstruction is spasmodic, because, as in the well-known phenomena of "dead finger," it may pass away and leave no effect behind it. If, on the other hand, the spasm persists for some time, nutritional changes, which, however, are entirely secondary, will ensue.

Such being the etiology of the local asphyxia, let us glance at its relationship to other diseases as depicted by Raynaud.

Thus he mentions (p. 72) a case in which the blood was examined, and showed diminution of red cells and increase of white cells, and remarks that this led M. Simon to class the case under the head of leucocythæmia.

Raynaud, however, questions whether leucocythæmia is a disease at all (p. 74), but suggests rather that it is but one symptom of a blood change which has as its results, on the one hand, local asphyxia, and on the other diminution of red cells, increase of white cells, and hypertrophy of the spleen and glands.

I may say at once that this is a view which recommends itself very strongly to my mind, and indeed I had already (*Lancet*, March 1892, p. 663, and elsewhere) given a similar explanation of the facts before I was aware of this passage in Raynaud's thesis. And I have pointed out that in my case (Eliza H.) an examination of the blood during some of her attacks, accompanied by hæmoglobinuria, which was made by my colleague Dr. S. W. Wheaton, showed increase of white cells, diminution of red cells, and increase of coagulability; and I shall presently give my reasons for believing that these blood changes are the results of the presence of an excess of uric acid in the circulation.

It has been suggested by Dr. Hunter that the excess of uric

acid which I found in the urine in these cases was the result of the blood changes, and not the cause of them; but I have given (*Lancet*, previous reference), my reasons for not sharing this opinion.

The enlargement of the spleen mentioned by Raynaud is interesting (and it was also present in Dr. Southey's case), because I have found that in nearly all conditions where the spleen is enlarged (and indeed, as I have pointed out, many others have observed the same thing), there is an excess of uric acid in the urine and in the blood, and I have been led to infer that this excess of uric acid was the result of the conditions which produced the enlargement of the spleen, namely, malarial and other fevers, of which I shall have to speak presently; so that the enlarged spleen and excess of urates in the blood and urine may be mere modifications of that most common condition, post-febrile uric-acidæmia, which, again, is not uncommonly a cause of Raynaud's disease or allied conditions; so that the observed connection between this disease and leucocythæmia is completely explained.

The relationship of Raynaud's disease to menstruation and pregnancy is of considerable interest, though Raynaud only narrates one case in which the symptoms underwent a monthly exacerbation, and even here we are not told, as he remarks, whether the attack coincided with the period. I should myself, however, have very little doubt that this was the case, for I know of no physiological condition in which an excess of uric acid in the urine and the blood is more certain to be met with than in menstruation. (See pp. 122, 134, and 154.)

As a matter of every-day observation, all conditions which upset nutrition and interfere with the taking and absorption of food at once produce a fall in the acidity of the urine and an increased excretion of uric acid; and menstruation, even when normal, and much more so dysmenorrhœa almost invariably brings about these results; and we get as a consequence of the uricacidæmia so produced the mental depression, headache, fits, and other troubles from which women are so well known to suffer at these times. The same fact explains also why women so rarely suffer from gout till after the menopause, because this monthly plus excretion of urates prevents their stores and accumulations of the substance from becoming so large as they do in the case of men.

Raynaud, however, mentions a very good instance of the opposite effects of pregnancy; for just as menstruation lowers nutrition and increases the excretion of urates, so does pregnancy act as a stimulus to nutrition; up goes urea and acidity, and the excretion of urates is diminished—that is, excretion falls below formation, and urates are held back and retained in the body, and with this the blood is cleared of urates and the circulation goes on freely. Now Raynaud tells us (p. 48) of a woman who noticed that the complete disappearance of her symptoms was the first indication of commencing pregnancy.

He says that in this case menstruation had no effect on the trouble. Possibly this woman had but very slight menstrual troubles, but the common effects of menstruation on the cerebral circulation are met with every day, and are too obvious to be passed over.

Here again we can explain a whole series of phenomena; for if pregnancy thus causes a retention of urates in the body, just as do most fevers and a large number of drugs, such as mercury, opium, and others, about which I have written at length, when the pregnancy comes to an end, and urea and acidity fall owing to the interruption of nutrition which parturition occasions, there will be an excessive excretion of urates, the result of the previous retention, and we get what I have spoken of in the case of drugs as a rebound, not post-morphinal or post-febrile uricacidæmia, but post-puerperal uricacidæmia. The cause is in each case the same; the result is also the same. We get contracted arterioles, and the result of this, slow high-tension pulse, which may be irregular or intermittent; cold skin and extremities; scanty, it may be, albuminous urine; headache; mental depression, and even fits; and Raynaud (p. 130) mentions two cases of the disease as coming on after recent delivery.

See also the most interesting parallel which is here presented to us between migraine (the uric acid headache) and Raynaud's disease; for we read in Dr. Liveing's valuable work ("Megrim and Sick Headache," pp. 46-47) of a woman who inherited the complaint from her father, and "became subject after puberty to severe attacks of megrim, recurring at the monthly period, generally immediately after menstruation. She married at twenty and had a large family, and it is remarkable that throughout her pregnancies she has been perfectly free from the complaint, which has invariably returned after delivery."

It will be evident that we can explain completely every fact here mentioned. Both troubles are due to uricacidæmia, and the effect of menstruation and pregnancy on this is in every case the same. But in the one patient the uricacidæmia and the high tension it produced affected especially the intra-cranial circulation and caused headache. In the other, the contracted arterioles affected especially the extremities, and produced Raynaud's disease.

No doubt a series of anatomical and physiological, or even pathological, conditions determined in each case the locality to be most affected; but these are of little consequence, because, as I have shown, and can demonstrate at pleasure, if the blood is kept moderately clear of urates, neither kind of disturbance would take place or continue.

With regard to irregular pulse, Raynaud mentions several cases in which this was observed, and he regards it as a purely nervous phenomenon. I have pointed out, however, that my pulse never falters or flutters except when I am suffering from contracted arterioles and high tension, and also that this and other "nervous" phenomena do not appear when my blood is kept free from any great excess of uric acid.

As to fevers, Raynaud mentions (p. 55) the case of a woman who had some attacks of ague in March, and about the middle of April began to be very easily affected by cold, so that exposed portions of her body became pale and then slate-coloured.

In one of my cases the attack came after a fever, and in another it came in a period of extremely low nutrition, perhaps due to insufficient food; and I have suggested that Dr. Southey's case was also due to post-febrile uricacidæmia.

Now fever, as I have just pointed out in the parallel case of pregnancy, increases metabolism; the excretion of urea and of acid rises, the alkalinity of the blood is diminished, and as a result it is cleared of urates, and the excretion of urates in the urine is diminished to a corresponding extent; but the blood being cleared of urates, the arterioles are free to relax, and we get a quick, low-tension pulse, as is well-known. The urates are, however, not merely kept out of the blood; they are also kept out of the urine—that is, are kept back and retained in the body—and when the acidity falls at the end of the fever, out they come again, flooding the blood with an excess of urate, and producing

post-febrile uricacidæmia, with all its signs and symptoms, prominent among which are slow high-tension pulse and scanty urine; so that the relaxed pulse of fever and the tense pulse which follows it are the simple results of the altered metabolism through its effects on the quantity of urates in the blood. (See p. 106.)

As I have said, Raynaud mentions what I regard as most undoubted and independent signs of dilated and contracted arterioles without having himself understood their import, for on p. 99, in describing an attack, he tells us that the urine is small in quantity, and on p. 121 he says, "Quelquefois chaque accès se termine par une abondante emission d'urines."

Can anything be more simple than the explanation of this? Could anything prove more completely that contraction of arterioles is present at the time of the attack, and is subsequently removed?

An interesting case of this disease is recorded by Mr. D'Arcy Power in the *Lancet* (vol. ii., 1893, p. 249) in a girl aged 4 years and 8 months, and the patient's mother "volunteered the statement that before the attack the patient passed much more urine than usual." This diuresis no doubt corresponded with the mental well-being which in older patients is frequently noticed to precede headache or fits. (See pp. 122 and 133.)

I have pointed out that under all conditions, both in physiology and pathology, the excretion of water in the urine is from hour to hour and day to day inversely as the uric acid; and that as the urate excretion can be controlled by drugs, the excretion of water can also be controlled.

I have also pointed out that it has been shown that digitalis, which is well-known to contract the arterioles and capillaries, does by this contraction reduce, or even completely arrest, the flow of urine (see p. 93), and have suggested that a similar contraction of the arterioles of the kidneys by uric acid accounts for the inverse relation between water and uric acid in their excretion.

In Raynaud's disease, therefore, we have evidence not only that the arterioles and capilliaries are contracted in the affected part and over the surface generally, but we also know and have evidence that they are contracted in the kidneys in the fact recorded by Raynaud that the urine is scanty; and in the fact

that the attacks may come to an end with a diuresis we have evidence that the vessels are dilated not only in the affected area and the skin generally, but also in the kidneys.

I would also point out the interesting parallel which these facts bring about between the attack of asphyxia on the one hand, and the uric acid headache, epilepsy, and hysteria on the other. In all of these the attack is contemporaneous with a scanty secretion of urine, and is followed by more or less diuresis; and in all the results are due to the same cause: the improved intra-cranial circulation which removes the neurosis is contemporaneous with an improved circulation in the kidneys which allows of a diuresis.

But if Raynaud had investigated any of the other secretions, they would have told him the same story, for the saliva is scanty, at the same time, and for the same reason, that the urine is scanty; and I see good reason to think that the gastric juice, the bile, and the other secretions are similarly affected. Nor are we without similar evidence in respect of other organs, for in all my three cases, and to some extent also in Dr. Southey's, the headache, mental depression, and bad temper which accompanied the attacks, gave plenty of signs that the intra-cranial circulation was far from satisfactory; and in the case of Eliza H., when drugs appeared to prevent her attacks, one of the most marked concomitant signs was a very decided improvement in temper.

The fact is that in uricacidæmia the vessels all over the body are contracted, and all the most important organs and tissues give evidence that their functions are thereby disturbed; and the relation between Raynaud's disease and certain neuroses, such as hysteria, epilepsy, and the headache and mental depression of which I have spoken, amounts simply to this, that they are all effects of uricacidæmia, and for this reason often occur together; and these disturbances, which seemed to Raynaud to show that the nervous system had some hand in the causation of symmetrical gangrene, merely prove that the disturbance of circulation which produces the gangrene in the extremities produces also such changes in the intra-cranial circulation that certain contemporaneous changes in the functions of the great nerve centres result.

What these changes will be depends in any given case on a variety of other general and local conditions, in addition to the uricacidæmia which is common to all, and will vary according as

the local conditions tend to favour or counteract the effects of the uricacidæmia on the local circulation.

I quite believe that there are people "whose heads have never ached," but it would not at all follow that they had never had uricacidæmia, but rather that the conditions of their intra-cranial circulation were such that high arterial tension disturbed them but little; in others, again, the local conditions might favour circulatory disturbance by high tension, and these would suffer with headache even in slight uricacidæmia; and the local conditions giving rise to these differences of effect may be anatomical, physiological, or pathological.

Syphilis is mentioned by Raynaud as an antecedent in two cases, and there was a history of congenital syphilis in the father of Dr. Southey's patient; and this, it seems to me, is just one of those things which may so alter local conditions as to render parts previously enjoying immunity liable to the worst effects of uric-acidæmia and the high tension which it produces.

Thus syphilis may produce such changes in bone membranes or intra-cranial contents as will make all the difference between uricacidæmia and high tension seriously affecting the intra-cranial circulation and hardly affecting it at all; and, similarly, in the extremities syphilis may produce such changes in the vessels as may make the difference between mere cold hands or "dead finger" and a regular attack of Raynaud's disease, the uricacidæmia being the same in both cases.

It will be evident, then, that in claiming Raynaud's disease as an incident in uricacidæmia, I by no means seek to exclude other factors which may both intensify the action of the uric-acidæmia and determine the locality which shall suffer most.

Indeed, I think it is very probable that the preponderance of girls and women among the sufferers from Raynaud's disease is due to their having less muscular power and activity than males of the same age; for there can hardly be any doubt that any weakness of the left ventricle would greatly increase the evil effects of contracted vessels on the nutrition of the extremities.

Opium was the drug of which Raynaud made most use in treatment, and he raises the question of its action on the muscular fibres of the arterial coats, the relaxation of which is his chief object. He mentions Pott's unbounded confidence in it

for the cure of gangrene, but seems to think it is of use chiefly as a narcotic.

I have shown that in conditions of uricacidæmia and high tension, opium relaxes the arterioles and produces diuresis by raising the acidity and clearing the blood of uric acid (see pp. 31-34); and this action of opium causing storage and retention of urates in the body is followed, just as in the parallel cases of fever, pregnancy, and the seasonal variations in excretion mentioned above, by a rebound; and we have, as the action of opium comes to an end and the acidity falls, not a post-puerperal or a post-febrile uricacidæmia, but a post-morphinal uricacidæmia; and I have also shown with regard to this latter, that if the urate is removed by a few timely doses of a salicylate, the post-morphinal uricacidæmia, with all its signs and symptoms (slow high-tension pulse, scanty urine, headache and mental depression), fails to appear. Exactly the same thing applies also to post-plumbic and post-mercurial uricacidæmia.

I believe that to a very considerable extent post-febrile uricacidæmia with its results might be prevented by a similar use of salicylates during the fever.

Here, then, we have a disease which, like those mentioned in previous chapters, is paroxysmal in relation to the more or less natural fluctuations in the excretion of uric acid, and we see reason to believe that it holds this relation, because it is due to the spasmodic contraction of capillary vessels which an excess of uric acid in the blood produces.

We have seen that Raynaud's disease affects especially the superficial structures and the extremities, and after this I need not go into any great detail to suggest that many minor changes in the nutrition of the skin are similarly related to the effects of uric acid on its circulation.

If this is so, we have at once a simple explanation of a large number of points in the cause and cure of skin diseases.

Thus the relation between erythema and urticaria on the one hand, to acute rheumatism on the other, may be explained by supposing that the skin trouble corresponds with the excess of uric acid in the blood, while the arthritis corresponds with the driving of that same uric acid out of the blood into the joints; thus it is not uncommonly seen that when a patient suffering from psoriasis develops articular gout the skin trouble disappears,

and the same with rheumatism, the erythema and the arthritis do not generally originate together. (See *Lancet*, vol. i., 1888, p. 523.)

Then we all know the relationship between dyspepsia and certain eruptions, or, again, between menstruation and eruptions; and in both these conditions, as I have shown, an excess of uric acid is almost certain to be met with in the urine and the blood.

Then, again, fevers are followed by post-fibrile uricacidæmia, with slow high-tension pulse, mental depression and subnormal temperature, and in this condition, just as we should expect, boils and papular eruptions which are very prone to ulcerate and slow to heal are often met with, and I have myself seen quite a number of such cases after typhoid fever and pneumonia in the last few months.

Alopecia again is not a very uncommon post-febrile symptom, as I have seen and read of, several cases in the last few years (see *British Medical Journal*, vol. i, 1890, p. 1027 and 1239), and a case which I recently saw myself had this very suggestive connection with season, that while the hair had on several occasions grown during the autumn and winter, it had fallen off again in the following spring. After what I have said as to the seasonal variations in uricacidæmia and the excretion of uric acid (p. 15), I will only point out that this case of alopecia parallels in the most striking manner the uric acid headache, mental depression, asthma, and phthisis, as well as the disease we are specially concerned with in this chapter, and I cannot but think that community of causation lies at the root of this parallelism.

Then again we can easily understand how such drugs as acids, opium, the iodides, calomel and thyroid gland or extract (Dr. Davies', *Lancet*, vol. ii., 1893, p. 399) act in curing these skin diseases, for all these substances have the one point in common, that they clear the blood of uric acid. (See chapters iii. and iv., also *British Medical Journal*, vol. i., 1888, p. 27, and vol. ii., 1892, p. 165, and *Lancet*, vol. ii., 1888, p. 63.)

And as I have said, I have for some time been in the habit of treating skin troubles originating in connection with any of the above-mentioned disturbances of nutrition with drugs which clear the blood of uric acid, and I think with considerable success.

Then if the vessels of the skin are contracted by uric acid so that surface temperature is reduced and even the nutrition of the

skin is eventually affected, it is probable that in those capillary vessels where the circulation is absolutely at a stand, the very walls of the vessels themselves will suffer in their nutrition and deteriorate, so that when the blood again passes into them they may bulge and leak, and thus small extravasations of blood result.

In this way I think purpura may be connected with uric acid, and the changes it produces in the circulation, and this will explain its connection with the rheumatic group, and also with chronic Bright's disease, dyspepsia, post-febrile conditions and menstruation. (See *British Medical Journal*, vol. i., 1890, p. 596, and *Lancet*, vol. i., 1891, p. 658, and vol. ii., 1891, p. 933, and *British Medical Journal* epitome, May 1893, p. 80.)

We have seen (p. 218), that Raynaud did not favour the idea that the troubles he described were due to local nerve lesions or neuritis, and probably the only relation between Raynaud's disease and peripheral neuritis is that both may be due to uric acid. (See p. 194, and also Dr. Buzzard's opinion in the *Lancet*, vol. ii., 1893, p. 1,233.) I have myself also heard from Dr. Mackie, of Lowdham, Notts, and others, of cases of neuritis which evidently had important connections with uric acid.

The only indication for the treatment of this group of diseases is to clear the blood of uric acid as quickly and as completely as possible.

CHAPTER XII.

Paroxysmal Hæmoglobinuria and Anæmia.

It was the clinical observation of cases of paroxysmal hæmoglobinuria and certain special forms of anæmia that first suggested to my mind the possibility that these troubles, as well as anæmia might be due to the presence of excess of uric acid in the blood.

I shall first of all, therefore, mention some of these cases and the results I obtained by investigating them.

December, 1888.—John H. McL., age 4 years and 10 months, said to be subject to attacks of cold and shivering, in which he passes red water.

Is generally extra well for some days before the attack, but his bowels are constipated (extra well means retention of uric acid; note the parallel here of what occurs in the headache and epilepsy of uric acid).

Just before attack he yawns a great deal (uricacidæmia).

His water on the day after the attack is quite clear again.

December 10.—His mother brought him to my out-patients today saying that he has an attack coming on. Has been taking cod-liver oil and steel wine for the last week. Was this a rebound after the iron?

He is pale and his hands and forearms are cold. Seems dull and heavy, shivering (?). Pulse slow.

I told his mother to sit in front of the fire with him; and in half an hour, at 3 p.m., she came back with the child, and brought some reddish urine he had passed. His face was flushed, and he seemed dull and heavy and said he had a headache; pulse now quicker. His mother says his bowels have not been open for two

days. He does not get these attacks unless he is exposed to cold in some way.

The specimen of urine was reddish-brown, clear, 1024, shewed the spectrum of oxy-hæmoglobin, and also that of acid hæmatin, the latter being removed by addition of ammonia. Under the microscope numerous pigment granules, some epithelium, fairly numerous shadowy blood-cells, also numerous granule and pigment, speckled casts. No oxalates. Urine, after boiling and filtering, gave urea 1.5 per cent., and uric acid .06048 per cent. Uric acid to urea 1 to 15. There was, therefore, an excessive excretion of uric acid, and probably as the child did not pass water before the attack began this was a mixture of the urine in the bladder before the attack, with that excreted during the attack, or the uric acid would have been higher still.

With regard to this case, I have very little doubt that it was a uric acid storm. He was extra well for a day or two before the attack, just as in uric acid headache and epilepsy (retention). The attack itself comes at a time—3 p.m.—when there is normally a plus excretion of uric acid (second, or afternoon alkaline tide); all the signs and symptoms of the attack are those of uricacidæmia; and lastly, in the blood-stained urine itself we find excess of uric acid. Unfortunately, this child never returned again, so that I could not investigate the matter further.

For comparison with this, I will now give a few notes of the case of a member of our profession, who consulted me on account of uric acid headache.

May, 1888, G. F. T., age 33.—In practice in a Midland county; works hard, lives plainly, fair amount of exercise and riding, occasional hunting. Father has slight attacks of gout, mother rheumatic and two years ago had peliosis rheumatica.

Previous health.—Slight rheumatic fever nine years ago; occasional joint pains since that; four and a-half years ago had rigors and dyspnœa, and was ill three months. Has always suffered from headache, but worse the last four years, sometimes now one every week. He has the pain on waking in the morning, and it remains the whole day. Taking wine at dinner always gives a headache next morning. His pulse, as observed by his assistant, is slow and of high tension during the headache. He suffers also from depression and irritability, and has cold extremities and rigors during the headaches.

Here there is a strong family history—gout on one side and rheumatism on the other, and nearly every possible sign of excess of uric acid in his own blood or joints. And now we come to the part that bears upon our subject. Also occasionally when he gets cold he has a rigor and a temperature of 102°, sometimes with joint pains, and passes smoky urine. In the autumn of this year he had such an attack after being out hunting and getting cold, and he kindly sent me some of the urine; unfortunately the notes I have of its examination are not very precise, and I was only able to examine it forty-eight hours after it was passed. It was acid, contained a slight excess of uric acid, fairly numerous blood-cells and some oxalate crystals, and gave the oxy-hæmoglobin spectrum. He himself considered that these were attacks of paroxysmal hæmoglobinuria, but I do not attach great importance to my examination because the urine was not fresh, and I think that the oxalates were possibly formed out of uric acid and diminished its apparent quantity. (See p. 255.)

Compare also a short note of a case that came to Dr. Brunton's out-patients at St. Bartholomew's, which he kindly allowed me to examine. April 25, 1890, Edward W., age 35.—The case was diagnosed as paroxysmal hæmoglobinuria, and I was given a small specimen of the urine and took a trace of his pulse; its rate was 112, and yet, in spite of this, the trace showed considerable tension, as the predicrotic wave was fairly well marked in the down stroke, the predicrotic notch was a considerable distance above the base line, and the dicrotic wave only of moderate size. The second sound of the heart was markedly loud. We were here probably just at the end of the cold stage and the beginning of the fever.

The urine was like pure blood, but showed no blood discs under the microscope, and after removal of albumen it yielded urea 1.4 per cent., uric acid .12768 per cent.; relation 1 to 11—an enormous excess of uric acid, and a relation to urea which it may be said is practically never met with in health.

I will here also mention a case which, more than any other, opened my eyes to the probability of uric acid producing destruction of red cells and so anæmia.

July, 1889, a lady, age 46.—A patient under the care of Dr. Brunton, during whose absence from home I saw her. Had a gouty family history, but never had gout herself.

She complained that she had "anæmic attacks" which she was sure were connected with gout. Said she lived a healthy out-door life, and often played cricket with her children, now growing up.

Her face was tanned by exposure to the sun; but through this and also in tongue and gums there was every sign of intense anæmia; I felt sure that she must have had a hæmorrhage, and suggested loss of blood by piles—which she had to a slight extent—or by excessive menstruation; these, however, she denied, and maintained that she had suffered off and on from this anæmia, which came in attacks, and was in some way connected with gout. So far as I could make out from her description, the attack after which the anæmia appeared was of the nature of a bilious attack, or sick headache; but she had no hæmaturia. Have we here hæmoglobinæmia not sufficient to cause hæmoglobinuria, but perhaps lasting over a longer time and producing the intense anæmia which I saw?

This, of course, raised in my mind the question, is uric-acidæmia a cause of more or less destruction of red cells, and does it in this way bring about more or less chronic and recurring anæmia? And having once been led to regard anæmia from this point of view, I was not long in coming on what have appeared to me to be other signs of the possible production of anæmia by uric acid. I have also pointed out in my previous writings that the injection of creatinin into the blood had been shown to produce destruction of red cells. (*Comptes Rendu de la Soc. de Biologie*, 1877.)

Aug. 12, 1890, Daniel H., age 10.—Admitted under my care in the Metropolitan Hospital. Complains of pallor, sleepiness and pains in the head. Father and mother well, five brothers and sisters well. Jaundice as an infant; measles also as an infant. Had a pain in his head on Aug. 1, and a pain in his right side on Aug. 7. Pallor gradually increasing but much worse the last two weeks.

Is now poorly nourished and pale even to bloodless. The conjunctivæ have a slight lemon tinge. Appears intelligent, but is dull and depressed. Pulse 120. Temperature 100°. There is a systolic murmur all over the cardiac area. The spleen is greatly enlarged, the notch being felt at or below the umbilicus, and the lower edge is level with the anterior superior spine of

the ilium. Blood shows increase of white and diminution of red cells. He was given liq. arsenicalis ♏iii., to be gradually increased. During my absence for a holiday he came under the care of Dr. Rolleston, who increased the arsenic to ♏viii. and eventually to ♏xii. and added a little digitalis, and on Sept. 17, pil. ferri carb., gr. v., was given twice a day.

On my return in the fourth week of September the child was worse than when admitted; he was not only very pale, but was weak and hardly able to sit up in bed. I got a specimen of twenty-four hours' urine and found it to contain a great excess of uric acid, 1 to 13.8, and this suggested to me that his dulness and general misery were due to uricacidæmia, which no doubt he had to a very serious extent, even if the severe anæmia was not also due to it; at any rate I felt that I knew nothing about the causation of splenic leucocythæmia, and would therefore treat the uricacidæmia, for which I might be able to do something. (See also p. 219.)

On Sept. 26, the note of the house physician, Dr. Stanley, was: "Still has some pain; extremely anæmic; spleen if anything, larger. Hands always tremulous. Pulse 126."

Sept. 30 I found him in the same condition lying weak and dull in bed. I accordingly stopped all the previous drugs, and gave a mixture containing ♏x. of dilute nitro-hydrochloric acid three times a day before meals, and another mixture containing sodii salicyl. gr. x., sp. am. arom. ♏xv., three times a day after meals, with the object of affecting the uricacidæmia.

Blood examined to-day (that is, before treatment) shows 10 red and one white cell to a micrometer square. Blood examined by Dr. Stanley.

Oct. 7.—Dr. Stanley's note is: "Colour much improved, less tremulous." And this was the beginning of a steady and continuous improvement, so marked and so unexpected as to surprise all who saw him.

Oct. 14.—Weight 3st. 11lbs. Abdomen 25½in. at umbilicus.

Oct. 20.—Blood much better in appearance, shows 35 to 40 red cells per square.

Oct. 21.—Bright and cheerful; up and about, and goes out. Has some colour in face now. Weight 3st. 13¼lbs. Spleen (?) smaller.

Oct. 29.—Weight 3st. 12lbs. 13ozs.

Oct. 31.—Spleen smaller and more to the left; the notch is

now one finger-breadth above the umbilicus. Abdomen 24½in. at umbilicus.

Nov. 12.—Continued improvement, same drugs. Weight 3st. 13lbs. 2oz. Spleen same.

Nov. 14.—Blood 23 red and 1 white cell per square. All medicines suspended.

Nov. 18.—Weight 3st. 13lb.

Nov. 26.—Acids and salicylate begun again.

Nov. 29.—Red cells 35 per square. Splenic notch two fingers'-breadth above umbilicus.

Dec. 6.—Red cells 29 per square. Pil. ferri. carb., gr. v., given twice a day in addition to other drugs.

Dec. 13.—Red cells 45 per square.

Dec. 17.—Weight 3st. 12lbs. 6oz. Going on well; seems bright. Abdomen at umbilicus 23in.; spleen much smaller.

Dec. 20.—Bright and well. Red cells 37 per square.

Jan. 17, 1891.—Same treatment continued. Red cells 38 per square. White cells not in excess, only one or two in the field. Weight 3st. 13lbs. 10oz.

After this he continued very well and was allowed to go home.

I am aware that cases of splenic leucocythæmia have improved on various treatments, or have got well in spite of treatment; but the result in this case followed so immediately on the alteration of treatment as to impress all who saw the case with the belief that it was not a coincidence merely.

Since this I have seen several cases of severe anæmia in young women, which resisted iron given in the ordinary way (generally pil. ferri carb. in increasing doses) for several months; but improved at once and decidedly on a course of salicylate of soda; and this drug has always seemed to affect their spirits and general condition in a remarkable way, leaving no doubt in my mind that they had been suffering from severe uric-acidæmia.

With regard to the way in which the salicylates produced this improvement, I shall have something to say when I come to demonstrate my curves, and similar treatment apparently prevented attacks of paroxysmal hæmoglobinuria and Raynaud's disease. (See p. 210.)

Lastly, I was led to notice, as the result of my previous ex-

perience, that, in a large number of cases of chlorosis or anæmia in young women, more or less dyspepsia, or even a bilious attack, as in the lady above mentioned, occurring especially at the menstrual periods, held an important place in the history of their trouble, and I knew well that these gastric disturbances meant a fall in urea formation and excretion, a fall in the acidity of the urine, and a corresponding rise in the alkalinity of the blood, so that this fluid at once became a better solvent of uric acid and its compounds, and at once took them up in solution from all points of deposit in the body. (Liver, spleen, fibrous tissues and joints.)

In a word, the dyspepsia produced uricacidæmia, and everything seemed to make it probable that the uricacidæmia produced the blood destruction and anæmia.

Then in the case of Raynaud's disease, with paroxysmal hæmoglobinuria, the notes of which are given in the previous chapter, my colleague, Dr. S. W. Wheaton, kindly examined the blood, and found on several occasions, corresponding with the hæmoglobinuria attacks, a diminution of red cells, an increase of white cells, (see p. 219 and 220), and an increase of coagulability.

Dr. Wheaton has also given (*Transactions of the Pathological Society*, vol. xlvi., p. 168) an interesting account of the pathology of the "Blackwater" fever of West Africa, which appears, as he shows, to have many points of resemblance with paroxysmal hæmoglobinuria; and I should have little doubt that it represents the effect of severe malarial fever on the excretion of uric acid, and so indirectly on the blood (see p. 106 and 217), and it is interesting to note that malarial fever is known to be a potent cause of "lithæmia" (see my paper in *Brain*, 1891, p. 73) and of Raynaud's disease (see p. 222).

There thus seemed to me to be a considerable accumulation of facts tending to show that in paroxysmal hæmoglobinuria, splenic leucocythæmia, chlorosis, and anæmia, there is at the time of the blood deterioration a considerable excess of uric acid, both in the urine and in the blood; in the urine I have found it in excess, and in the blood it gives rise to signs and symptoms which are practically identical with those of the uric acid headache. (See chap. vi.)

Then, again, in several of these disease conditions, a drug (salicylate of soda), which eliminates uric acid, and prevents its being present in excess in the blood, appears to produce more or

less marked improvement, even when iron or arsenic have failed, while dyspepsia, which brings excess of uric acid through the blood, does harm.

At this point in my investigation the writings of Horbaczeuski, and a lecture by Prof. A. E. Wright, were published, and I therefore said in a letter to the *Lancet* (vol. i., 1892, p. 663) that it appeared to me that these investigators were really mistaking a cause for an effect; and I gave my reasons for thinking that the excess of uric acid which they noticed in the blood and urine at the time of certain blood changes was the cause of those blood changes, and could not well be their effect.

I said further that in the case of paroxysmal hæmoglobinuria, it could be proved that the excess of uric acid in the blood and urine at the time of an attack was not the result of the blood changes because it was the result of a fluctuation in urate excretion (minus excretion or retention) which began hours before there were any blood changes.

In this respect also the excess of uric acid in paroxysmal hæmoglobinuria has an identical causation with the excess in the paroxysmal headache, the paroxysmal fits, and the periodical mental depression described in previous chapters; and in all these alike the fluctuation in the excretion of uric acid is the cause of all the signs and symptoms, and not their result.

At the time my paper on a case of Raynaud's disease was read before the Medical Society (see *Transactions*, vol. xv., p. 156), Dr. Hunter, whose investigations on the blood are well known, said: "In a number of the diseases of the blood of a destructive nature, such as leucocythæmia and pernicious anæmia, the uric acid was greatly increased; there was evidently a direct connection between the two, and he felt sure that the appearance of the uric acid was a result, and was not to be regarded as standing in a causal relation to these diseases." I am glad to see that Dr. Hunter is at one with me as to the facts, and further considers that there is a direct connection between them; but I hope presently to be able to demonstrate that the connection is just the reverse of the one he suggests.

All these facts then seemed to render it very probable that uric acid was the cause of these blood changes both in paroxysmal hæmoglobinuria and anæmia.

But I have complete power over the excretion of uric acid in

the urine, and if anyone will chalk out a curve on the wall which he wishes his urate excretion to follow from day to day, I will undertake to make it follow a very similar curve, provided he follows my instructions as to diet and drugs that affect the solubility of the substance.

But the excess of uric acid above the relation to urea of 1 to 33 represents, I believe, the amount of uric acid that passes through the blood each day; thus when the uric acid curve is above the urea curve by two or three grains, two or three grains passed through the blood that day. (See p. 12.)

It follows that if I have complete power over the curve of excretion I have also complete power over the amount that can pass through the blood, and if uric acid causes the above mentioned blood changes I ought to be able to produce, if not an actual attack of paroxysmal hæmoglobinuria, at least such blood changes as occur in anæmia.

But we have seen in chapter iii. that uric acid taken pure by mouth passes straight into the blood (which was to some extent known before), and will in due time pass out in the urine in quantity which is roughly proportional to that swallowed.

The only essential condition of this direct absorption and excretion of uric acid is that the blood shall be kept in such state as favours or at least does not hinder the solubility of urates; and this can be fulfilled by so ordering the diet as to prevent the alkalinity of the blood being diminished.

It is thus possible to increase the uric acid passing through the blood by the simple process of administering it pure (in powder grains 1 to 2 ter.) by mouth; leaving diet and all other factors unchanged.

But those who have from diet and other causes but a slightly alkaline blood must not expect to increase the uric acid it contains very much by taking it by mouth, for though it gets into their blood it will quickly be driven out again into their fibrous tissues and organs where it will remain till the blood becomes favourable to its solubility.

And in no one (unless the blood is very alkaline) will there be much excess of uric acid in the blood and urine on the day a dose of uric acid is taken because uric acid itself diminishes the alkalinity of the blood, and interferes for a time with its own solubility (see p. 65); but on the second or third day after a dose when

the alkalinity of the blood has again risen uric acid will begin to be present in excess in the blood, and to pass in excess in the urine, and such excess will correspond more or less in extent and duration to the dose taken. (See also *Journal of Physiology*, vol. xv., p. 167.)

Our problem then is this. Many disease processes in which there are important blood changes appear to be contemporaneous with the presence of an excess of uric acid in the blood and urine, and there are reasons for supposing that the uric acid may be the cause of the blood changes: does the intentional production of an excess of uric acid in the blood bring about any similar blood changes?

On this point I shall allow my curves to speak for themselves with such small explanation as may be necessary.

Before giving them I will say that I have used for this investigation the hæmoglobinometer and hæmocytometer of Dr. Gowers, and have followed as closely as possible the directions issued with the instruments.

The blood decimal is the result of the fraction $\frac{\text{per cent. hæmoglobin}}{\text{per cent. red cells}}$ or if normal $\frac{100}{100} = 1.0$, and all smaller quantities are represented by decimals as in the following curves; and I agree with Dr. A. E. Garrod, Dr. Wilcox, and others (*Proceedings of the Royal Medical and Chirurgical Society*, February 9, 1892), that this is the safest guide to the condition of the blood, representing as it does the hæmoglobin value of the individual cell: for the absolute quantity of cells and hæmoglobin varies greatly according as the blood is concentrated by diuresis, or is diluted by retention of fluid in the body,[1] but these things cause no variations in the value of the blood decimal which again can easily be represented in a curve, for comparison with the curves of the urate excreted in the urine.

Fig. 29 represents the results of simultaneous examination of the blood and urine in myself, the blood being examined only every two or three days, and the urine curves being obtained by dividing the total excretions of three days by three so as to shorten the figure.

Notice here the general downward direction of the blood decimal curve and the general upward trend of the uric acid curve. The urea curve is given simply to show the height of uric

[1] See *Journal of Physiology*, vol. xiii., and *Lancet*, July, 1892.

acid above urea (the curves are super-imposed at the relation of 1—33) as the index of the probable amount of uric acid passing through the blood.

On Day 20 at the beginning of the figure, urea is close to uric acid so that little or no uric acid passed through the blood, and the blood decimal is fairly high = .71. On Day 23 uric

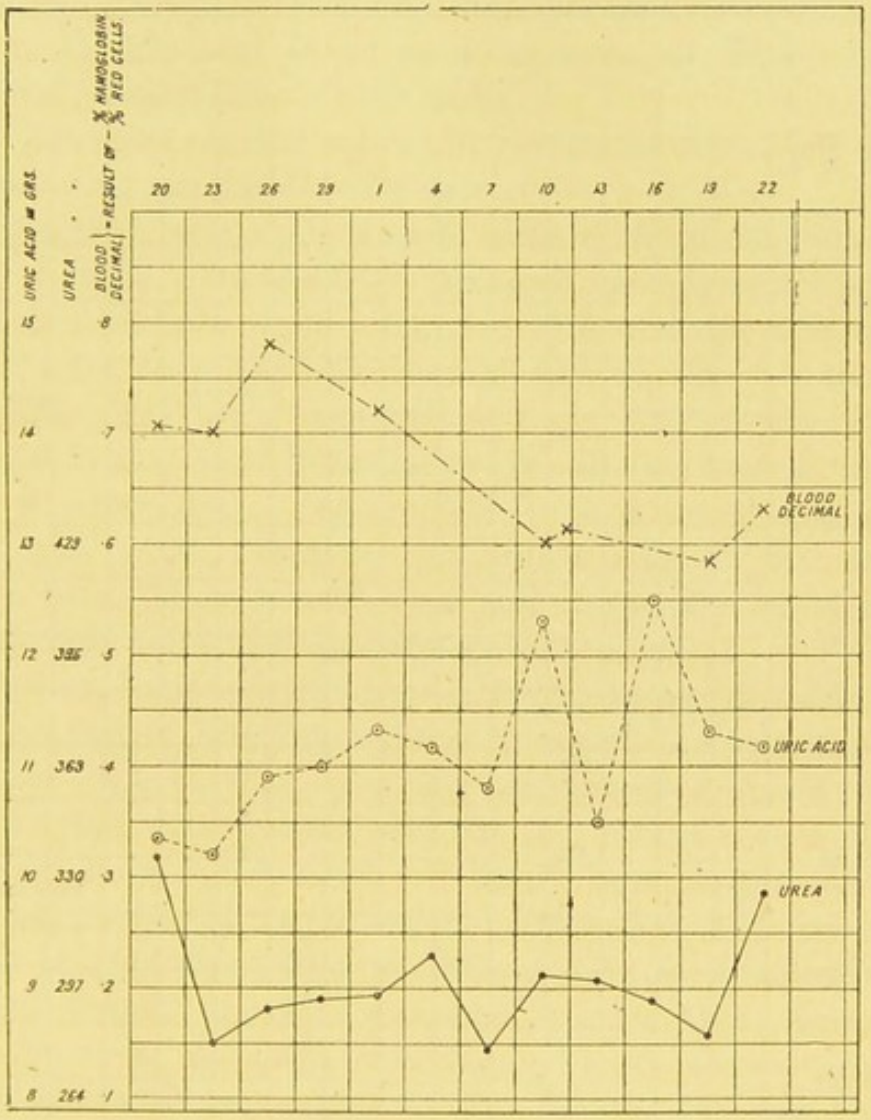

FIG. 29.—CURVES OF URIC ACID EXCRETION AND THE BLOOD DECIMAL.

acid exceeds urea by $1\frac{3}{4}$ grs., and this amount probably passed through the blood, and with this the blood decimal falls to .70. On Day 26 more than 2 grs. of uric acid passed through the blood, and yet the blood decimal rises decidedly to .78, but the explanation of this is probably that the blood was not examined sufficiently often to correspond with the excretion curves, for uric

acid was low on two days preceding the 26th, while a high rise on the 26th brought up the average in the blood for three days to 2 grs. per day. If the blood had been examined on the 25th, it would probably have been found above .8, a fall to .78 taking place with the high uric acid of the 26th. The blood is again examined on June 1, the uric acid in blood averaging meanwhile

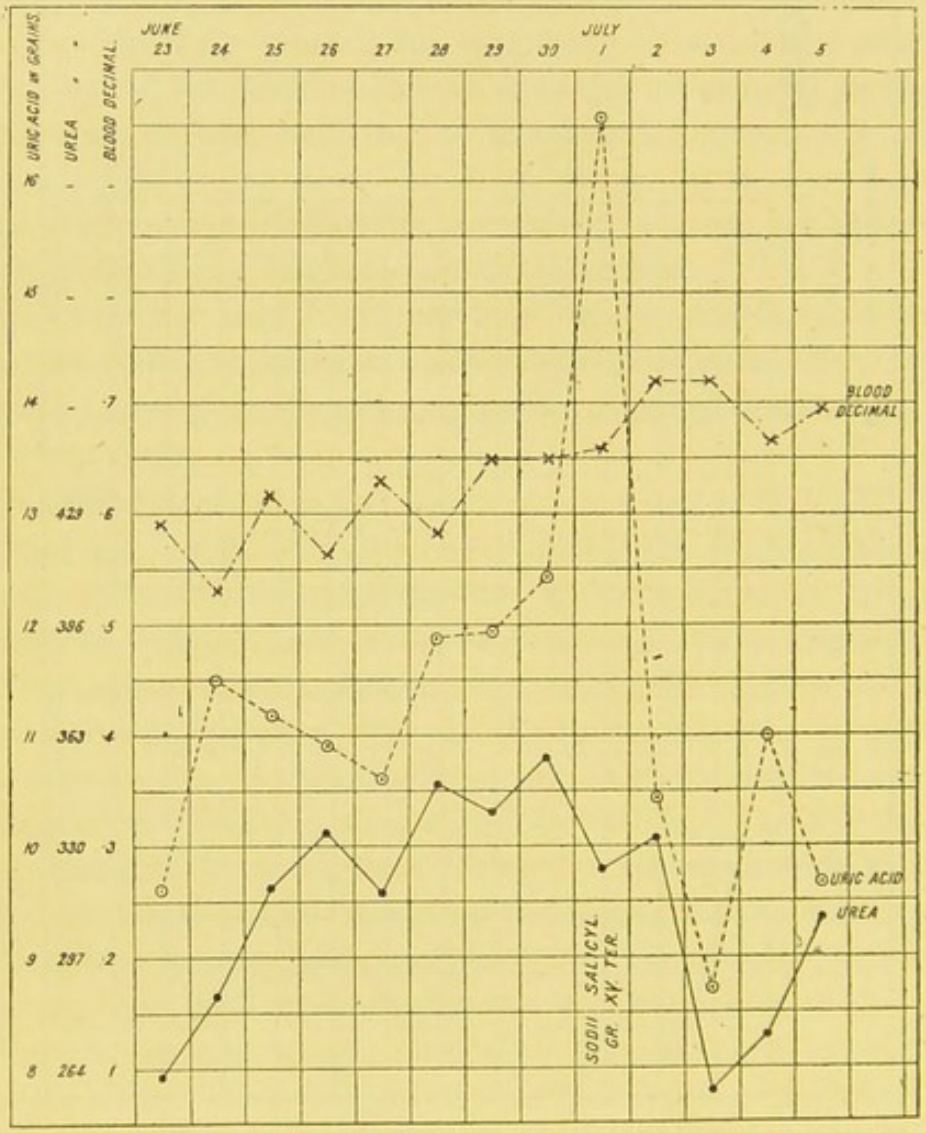

FIG. 30.—CURVES OF URIC ACID EXCRETION AND THE BLOOD DECIMAL FROM DAY TO DAY.

2 to 2¼ grs. per day, and with this there is a fall to .72. On June 10, with uric acid rising to 3¼ grs. per day, there is a marked fall of the blood decimal to .6; there is a slight rise on the 11th, corresponding to a fall of uric acid; and a fall of the blood decimal to .56 on the 19th in accordance with the passage of 3 to 3½ grs.

through the blood on the days from the 16th to the 19th. Lastly we see a rise of the blood decimal to .63 on the 22nd with a fall of the uric acid passing through the blood to 1¼ grs. per day.

This figure shows generally that the blood decimal is higher, the nearer the uric acid is to urea, *i.e.*, the less there is passing through the blood ; and lower the higher the uric acid is above the urea, *i.e.*, the more there is passing through the blood.

The high rises of uric acid on the 10th, and again on the 16th were due to uric acid taken by mouth on purpose to increase the amount passing through the blood.

Fig. 30 shows similar curves of results obtained on myself, the blood being examined every day.

On the 23rd, uric acid exceeds urea by 1½ gr. and the blood decimal is at .59. On the 24th, uric acid exceeds urea by 2¾ grs. and the decimal falls to .53. On the 25th, the uric acid exceeds urea by 1½ grs. only, and the decimal rises to .62. On the 26th, uric acid exceeds urea by less than 1 gr., and yet the decimal falls to .56, but it rises next day to .58, uric acid remaining still about 1 gr. above urea. On the 28th, with a rise of uric acid to 1⅓ gr. it falls to .54. Then on the 29th, it rises to .6 in spite of uric acid being 1½ gr. above urea, and it remains at .6 on the 30th, uric acid being still about 1½ gr. above urea.

On July 1, I tried an experiment, taking xv. gr. of sodii salicyl, with the object of bringing a lot of uric acid through the blood, and in this I was successful, as uric acid exceeded urea by nearly 7 grs. ; but the blood decimal did not fall, indeed it rose slightly to .61. On July 2, uric acid fell below urea, as the salicylate was left off, so that by hypothesis none passed through the blood ; and with this the blood decimal rose to .67 and remained there on the 3rd, though uric acid was about ¾ grain above urea. On the 4th, however, uric acid rose, being 2¾ grs. above urea, and with this the blood decimal fell to .61. On the 5th, uric acid fell again, being scarcely ¼ gr. above urea, and with this the blood decimal rose to .64.

The exceptions mentioned above only serve I think to show up the rule that uric acid, in relation to urea and the blood decimal, move in opposite directions. The exceptions are probably due to want of exact correspondence between the examination of the blood and that of the urine. The urine of the given date is the excretion of the 24 hours ending 7 a.m. on that date, while the

blood was examined at 11 a.m. each day. It is quite possible that a large amount of uric acid passing through the blood between 7 and 11 a.m. may depress the blood decimal more than the excretion of the previous 24 hours would lead us to expect, or a small excretion in those same hours might allow the blood to recover a little from the uric acid of the previous day.

That salicylate of soda could bring so much uric acid through the blood without depressing the blood decimal was rather a surprise, but I would point out that these large excretions under salicylates are not accompanied by the usual symptoms of uric-acidæmia. There is no headache, and but little mental or bodily depression, though if seven grains of uric acid had passed through the blood in combination with alkali, there would have been severe headache, marked mental and bodily depression, slow high tension pulse and scanty urine, and with these probably a marked fall of the blood decimal. (As in the case of the lady mentioned above.)

The rise of the blood decimal with the low uric acid the day after the salicylates is extremely interesting and illustrates probably the way in which these drugs did good in the case of splenic leucocythæmia mentioned above, and in several cases of simple anæmia and chlorosis in which I have also used them, when iron did not seem to act well; for, as we shall see presently, uric acid is more powerful than iron, and when both are present in the blood together, its decimal falls instead of rising.

It seems probable then that the good effects of salicylates are due to two things, first; that they rapidly clear urates out of the body without allowing them to do harm in passing through the blood; and second, that they thus, by elimination, free the blood from uric acid and allow the blood decimal to rise.

It is open for anyone to repeat these experiments, and it is not at all necessary to estimate the uric acid from day to day, because it can be inferred from the water with quite sufficient accuracy in accordance with my law of excretions—that the urinary water is from hour to hour, and day to day, inversely as the uric acid excreted along with it.

Let anyone who is going to try this collect all his urine for two or three days, and, say that it averages 1500 cc. a day, let him take gr. ii. of uric acid ter. for one day, and gr. i. ter. next day, still collecting his water.

On the days uric acid is taken the water will rise a little, say to 1600-1700 cc., for uric acid, as I have said, raises the acidity, interferes with its own solubility, and causes more or less diuresis; but a day or two later acidity will fall again if he does nothing to raise it, and with this there will be an excess of uric acid in the blood and urine, and the latter will be proportionately scanty, say 800-1000 cc., and if he examined his blood before he took the uric acid, and again now, he will find that with the rise of uric acid and the scanty urine the value of his blood decimal has fallen very decidedly.

I shall now go on to my other figures, showing some of the results I obtained in cases of chlorosis by causing excess of uric acid to pass through their blood.

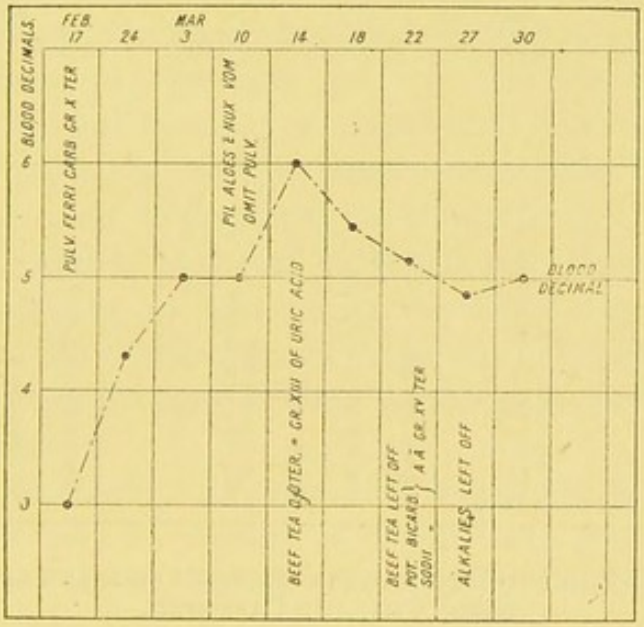

FIG. 31.—CURVE OF BLOOD DECIMAL IN CHLOROSIS SHOWING EFFECTS OF IRON, BEEF TEA, AND ALKALIES.

In these cases the urine was not collected, but no doubt the effects on excretion were the same as in my own case, and the administration of uric acid in one form or another always produced, as we shall see, immediate and distinct effects on the blood decimal.

Fig. 31 shows the curve of the blood decimal in the case of M. B., age 18, suffering from chlorosis. On February 17, the blood decimal being only .3, she was put on pulv. ferri carb., gr. x. ter., and the curve shows the rise of the decimal to .5

on March 10, and its further rise to .6 on March 14, after the iron had been left off. On the 14th half a pint of beef tea three times a day was added to her diet, and this beef tea was found on estimation to contain about 8.6 grs. of uric acid to the pint, and I may say that it seemed to be very strong and good beef tea; she would then take about 13 grains of uric acid a day.

On March 18 the blood decimal has fallen to .54, and on the 22nd, when the beef tea was left off, to .52.

I may point out in passing that uric acid given by mouth to those who, like anæmic girls, have rather low nutrition, is more likely to remain in solution in the blood, because their blood is probably more alkaline than that of better-nourished individuals;

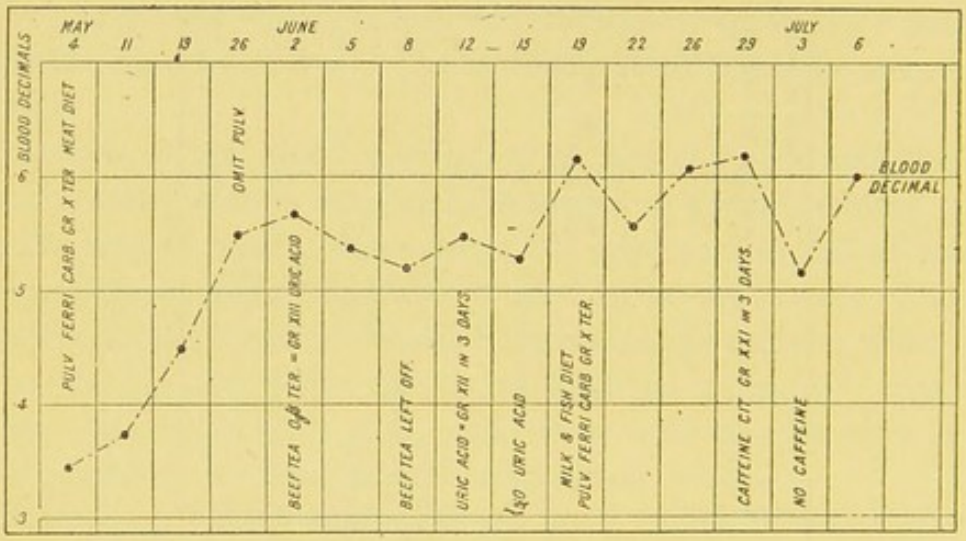

FIG. 32.—CURVE OF BLOOD DECIMAL IN CHLOROSIS SHOWING EFFECTS OF IRON, BEEF TEA, AND CAFFEINE.

therefore, the effect of giving uric acid is likely to be more marked in poorly-nourished individuals than those who are robust and well fed, and dose for dose the effect on the blood curve will be greater in the former than in the latter.

Though I stopped the beef tea on the 22nd, I gave the bicarbonates of potash and soda, 15 grs. of each, three times a day, with the object of increasing the urate in the blood, and we see on the 27th that the blood decimal has further fallen to .48. The alkalies were then left off, and on the 30th the blood decimal had risen slightly to .5.

I have no doubt that the whole of this fall was due to the uric

acid taken, for the general tendency is for the blood curve to rise slowly for a considerable time after the iron is left off.

Fig. 32 is the blood curve of E. E., age 23, also suffering from chlorosis. On May 4, her decimal being at .35, she was put on pulv. ferri carb., as in the previous case. On May 26, the decimal having risen to .56, the iron was left off. On June 2, when the decimal had risen to .57, she was given beef tea = 13 grs. uric acid per day, and this was continued till the 8th, the blood decimal falling on the 5th to .54, and on the 8th to .53.

On the 12th, four days after the last dose of uric acid, the blood decimal had risen again to .55. On this day, the 12th, she was put on the equivalent of 6 grs. uric acid for one day, and 3 grains each for the two following days, to try the effect of smaller doses, and on the 15th the blood decimal had fallen again to .53, so that the effects of a small dose were fairly marked, and I think that a small dose will, perhaps, get uric acid into the blood more quickly than a large one, for uric acid, as I have said, interferes with its own solubility, and the salts contained in beef tea will in a similar way tend to depress the alkalinity of the blood,[1] and cause the uric acid to be stored in the fibrous tissues and viscera instead of remaining in solution in the blood: and in producing changes in the blood decimal, we have not only to get it into the blood, but to keep it there so long as the kidneys will allow it to remain unexcreted.

On the 19th there is a remarkable rise of the blood decimal to .62, making it look as though it would have gone on rising all the way from June 2, but for the uric acid taken.

On the 19th, iron was again given in the same dose as before, and it was rather a surprise therefore, to find that on the 22nd, the blood curve had fallen to .57, but I had forgotten the fact that, on the 19th, the patient was not only put on iron, but also on a milk and fish diet, having previously been on meat, and the change of diet no doubt produced a fall of acidity, acting like the alkali given in the previous case; this brought some of the previously stored uric acid through the blood, and the uric acid overcame the iron, and produced a fall in place of a rise in the blood decimal.

A similar explanation can be given of a point in fig. 31,

[1] See p. 31.

which I omitted to mention. In this figure it will be seen that on March 10, the blood decimal failed to rise, though the iron was still being taken, and this, I think, was the result of some abdominal pain and digestive disturbance which was unfortunately produced by some aloes pills given her for constipation; the digestive disturbance no doubt produced uricacidæmia, and the uric acid, as in the other case, overcame the iron so far as to prevent a rise of the blood decimal.

By the 26th, however, (fig. 32), most of the uric acid has passed through the blood and been excreted, the iron then comes into action, and the blood decimal rises to .61. On the 26th, the iron is left off, but the decimal again rises on the 29th to .62.

On the 29th, citrate of caffeine was given, 9 grs. on the first day, and 6 grs. on each of two subsequent days. Now caffeine may for all practical purposes be regarded as uric acid, and my experiments on myself (fig. 18, p. 69) show that, like uric acid, it first raises the acidity and clears uric acid out of the blood, causing relaxation of arterioles and a diuresis; later, when the acidity falls, an excess of uric acid, proportional to the caffeine taken passes through the blood and into the urine;[1] and we see from the curve that caffeine brought down the blood decimal, just as uric acid does, for on July 3, we have a marked fall to .52, which is followed by a rise to .6 on the 6th, the drug having been left off.

I may say at once that these and other similar experiences, have left no doubt in my mind that just as iron runs up the blood decimal, uric acid brings it down; and that when the one is acting in opposition to the other, the uric acid is the more powerful. And this explains the fact noted by Murchison and others, that in some cases of anæmia iron will not act till the liver has been got into proper order; and the drug they most often used to get it into order was calomel, or other form of mercury; and mercury, as I have shown, clears the blood of uric acid. (See Murchison, "Croonian Lectures," *Lancet*, vol. i., 1874, p. 504, and fig. 11, chapter iii.)

Now, as soon as the blood is cleared of uric acid, the general metabolism, being freed from the incubus of contracted arterioles, goes ahead, there is a general rise of urea and acidity, which keeps the blood more or less clear of uric acid, and iron is then able to act and bring about permanent improvement.

[1] See also Prof. See, *Lancet*, i., 1890, p. 677.

I have every confidence that I can in this way do anything I like with the blood decimal, and that anyone who will take the trouble to repeat my experiments will get similar results.

In addition to the figures given above, I have examined my own blood and urine side by side every day for many weeks, and find that the changes are practically constant, and that with every marked rise of uric acid excretion the blood decimal falls, and *vice versa;* and indeed I would undertake to tell correctly, from a daily examination of the blood of a patient, whether the uric acid had risen or fallen each day, the urine being examined by someone else.

To conclude this part of the subject, I will just show a small figure, No. 33, which proves that others have obtained results which are practically identical with my own, without knowing how they were produced.

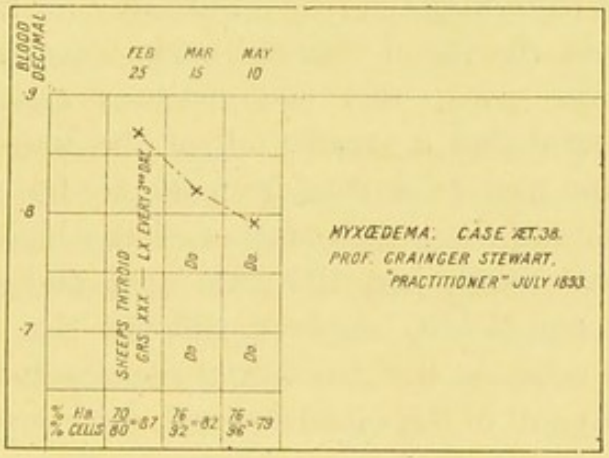

FIG. 33.—CURVE OF BLOOD DECIMAL SHOWING EFFECT OF FEEDING ON THYROID GLAND.

In my paper in the *Journal of Physiology*, vol. xv., I suggested that extracts of thyroids and other glands possibly owe no small part of their activity in myxœdema and skin diseases to the stimulant properties of the uric acid and other nitrogenous extractives in which they are known to be rich; and I can prove that in myself the taking of thyroid glands or a thyroid extract, carefully prepared for me by Messrs. Savory and Moore, produces results which are identical with those produced by so much uric acid (see p. 71); that is to say, there is a first stage of stimulation with rising acidity, well being, relaxed arterioles and diuresis (just as with caffeine also), followed later, when they are left

off, by falling acidity with plus excretion of uric acid, contracted arterioles and scanty urine, and with these latter a fall in the blood decimal, just as with uric acid taken in any other form.

It is interesting to note in this connection that myxœdema, like asthma, Raynaud's disease, and dropsy, is better during pregnancy, or during fever, and we shall have an instance of the effects of the fever of measles on the dropsy of Bright's disease in chapter xiii. Again, myxœdema, like certain skin diseases, may be worse at the menstrual periods, while arthritic troubles, which stand at the opposite pole of causation, tend to be worse during fever and may be better during menstruation. (See *Lancet*, vol. ii., 1893, p. 744; *British Medical Journal*, Epitome, September, 1892, p. 43, and *Ibid.*, February, 1892, p. 25.)

I was, therefore, much interested to see in the *Practitioner*, July, 1893, a paper by Prof. Grainger Stewart, in which he gives the blood factors in a patient who was being fed with 30 to 60 grs. of thyroid gland every third day for myxœdema.

Fig. 33 shows the blood decimal curve constructed from the figures which he gives, and demonstrates that this feeding with thyroids produced a steady fall of the blood decimal. It is true that the red cells rose from 80 to 96 per cent., but this is simply due to the concentration of the blood; for thyroid gland, as I have said, just like uric acid and caffeine causes diuresis; the hæmoglobin, however, did not rise proportionally, and on the last occasion it did not even rise absolutely, and so the result is a steady fall of the blood decimal, doubtless due, as in my own curves, to an excess of uric acid passing through the blood.

Professor Stewart's patient, it is interesting to note also, suffered very markedly with all the symptoms of an excess of uric acid in the blood; such as weakness and general soreness, with tightness and oppression in the chest, passing later into severe dyspnœa, with blood-stained expectoration; her asthmatic trouble being complicated by the presence of old disease of the mitral valve. (See chapter ix.)

It is now easy to understand the causation of chlorosis and anæmia, and their relation to dyspepsia and bilious attacks, for these disturbances cause excess of uric acid to pass through the blood; but there are other most interesting relations between the development of girls and the causation of these troubles, which furnish at least some explanation of the frequency with which anæmia is met with in young women.

Now, writers on the subject say that the greatest development in girls occurs about the thirteenth year, when they may increase as much as 10 to 11 lbs. in a year; after this, they fall gradually to a 2 lbs. increase in the seventeenth and eighteenth years. (See "Book of Health," Morris, p. 281.)

Now the 10 to 11 lbs. increase in the thirteenth year means a very active metabolism in the girl's organism, and with this there is high urea per pound, high acidity of the urine and low alkalinity of the blood, and the result of this last factor is a holding back and storage of uric acid in the body, in the liver, spleen, and probably other fibrous tissues. With this state of things would doubtless go an increased tendency to rheumatism, and this great fluctuation of metabolism may thus in part account for the greater liability of girls to acute rheumatism.

But the active metabolism is not continued, but gradually falls away down to 2 lbs. a year; and the result of the diminishing metabolism is falling urea and acidity, rising alkalinity of the blood, with increased solubility and excretion of the uric acid previously retained.

But just as these changes are in progress menstruation is established, and this almost invariably upsets digestion, and still further lowers metabolism; producing more or less severe uricacidæmia, the signs of which, slow high tension pulse and headache or mental depression are among the most common accompaniments of menstruation. (See chapter viii., where I have drawn attention to Dr. Barnes' remarks on the frequency of suicide in menstruating women, and also to the simple explanation which menstrual uricacidæmia affords of the headaches and fits which so often occur at the periods; for further facts see also a paper by Dr. Hunt, *Lancet*, vol. ii., 1880, p. 89.)

Add to this the fact that depression breeds depression, and that once the metabolism is depressed, uric acid tends to keep it down, so long as there is a supply of this substance in solution in the blood, to contract the arterioles and generally interfere with nutrition; and conversely as I have said, stimulation breeds stimulation, for if you clear the blood of uric acid for a few hours, metabolism will go ahead and keep it clear.

In young women then we have a storage of urate in their active metabolism at 13, and a passage of this urate through the blood as nutrition falls in later years, and especially with each recurrence

of menstruation. It is little wonder then that they suffer from anæmia, the wonder is rather that any of them should escape it.

Paroxysmal hæmoglobinura represents, I have no doubt, a similar but more acute fluctuation in the excretion of urates, probably often related to dyspepsia and gastric upset in exactly the same way that migraine epilepsy and Raynaud's disease, are related to it, and it is paroxysmal just as they are paroxysmal, in relation to the fluctuations in urate excretion.

Anæmia associated with enlarged spleen is doubtless related to the large quantities of uric acid met with in the blood and urine of these cases. (See pp. 219 and 233.)

The way in which the excess of uric acid in the blood is brought about I have already gone into; and as I have said above, the increase of white cells met with in these cases may be entirely secondary.

In the *Practitioner*, August, 1890, Dr. F. W. Mott wrote an interesting paper on the spleen as a centre of destruction of red blood cells, and it may be noted in this connection that Dr. Hunter (*Lancet*, 1892, vol. ii., p. 1318) points out that certain substances (toluylendiamine) which have a destructive action on the blood act far less powerfully after the spleen has been removed; and no doubt if uric acid destroys the blood elements, they are certain to meet it in concentrated solution in the spleen, and the facts just mentioned suggest strongly that the action of toluylendiamine is indirect.

The effects of fevers in producing anæmia are easy to understand, for they diminish the alkalinity of the blood and lead to a storage of urate in the body, and this, when the fever ends, finds its way back into the blood (see facts about pneumonia, pp. 47 and 106), causing post-febrile uricacidæmia with post-febrile bradycardia, high tension pulse, depression of mind and metabolism and subnormal temperature an identical sequence of events with those producing chlorosis. The excess of uric acid met with in the blood and urine after malaria and other fevers, with or without enlarged spleen, is thus, I believe, the result of the storage of urate that took place during the fever. (Compare also previous remarks on rheumatism in girls.)

In vol. lxxv. of the *Transactions of the Royal Medical and Chirurgical Society*, Dr. A. E. Garrod has an interesting paper on the anæmia of rheumatism, and the relation of the blood changes to the excretion of uro-hæmatoporphyrin.

In several of his curves, "worth," which corresponds with my blood decimal, remains steady or rises during the fever, and falls afterwards as the temperature becomes subnormal, that is to say, during the fever the urate is all in the joints, and there is none in the blood except in combination with salicylates (see previous remarks on the action of salicylates in anæmia); as the fever passes off there is post-febrile uricacidæmia with a fall of the blood decimal, just as we should expect when urates combined with alkali are passing through the blood; and in at least one of Dr. Garrod's cases, the "worth" fell at the end of the fever *in spite* of iron being given. (See also Dr. Garrod's remarks, previous reference, p. 191.)

He also notices a corresponding increase of white corpuscles, just as in the similar condition I have mentioned above, and as observed by Dr. Wheaton. I should expect a fall of the blood decimal just before the onset of the fever, when according to my explanation of the causation of acute rheumatism, there is sure to be an excess of uric acid in the blood (see chapter xvi.), but Dr. Garrod's statements are not very definite with regard to this point.

The effect of all fevers on the blood decimal is probably the same as that of acute rheumatism, and I found in a case of pneumonia, that at the time of the post-febrile uricacidæmia with subnormal temperature the blood decimal was .55, while a few days later, when the temperature had again gone up to normal, it had risen to .60.

It is, again, quite easy to explain the effects of hot weather and of tropical climates in producing anæmia, for heat increases the alkalinity of the blood and the urate it will hold in solution; and this will have most effect in those who eat meat, and so introduce much urate into their body; and least in those who live on vegetables and fruits, and so ingest but little uric acid. (See chapter xvii.)

The effects of diet also are well known and easily explained, for Dr. Mackenzie points out that meat diet increases the destruction of red cells (*Lancet* or *British Medical Journal*, vol. i., 1891), and others have pointed out that farinaceous diet does good, and that pale anæmic children are most common among the "well fed" upper classes (*British Medical Journal*, ii., 1890, p. 85,—in my opinion, "not wisely but too well" fed upper classes.

The paper which immediately precedes mine on anæmia in the

British Medical Journal, vol. ii., 1893, p. 670, is one with the heading "Preliminary Report on the Causes of Chlorosis," by E. Lloyd Jones, M.D., and this contains so many points of interest, and so many of which, I think, the causation by uric acid will be found to give a complete explanation, that I may as well mention some of them here.

Thus, Dr. Jones points out that after fifteen years of age the specific gravity of the blood falls in the female while it continues to rise in the male, and that this is the age at which girls become anæmic.

But if this anæmia and chlorosis is, as I am suggesting, the result of excess of uric acid in the blood, the causation of which at this time of life I have already gone into, it is not difficult to see that this uricacidæmia almost entails a fall in the specific gravity of the blood, because it prevents the outflow of water from it by any or all the glandular organs of the body.

It is easy for anyone to convince themselves in two or three hours' work that this is a fact; let them produce in any of the ways previously described so much uricacidæmia as shall markedly diminish the excretion of water in the urine, and watch the blood meanwhile; they will find that hour by hour as the urinary water diminishes the water in the blood increases; that is to say, there is a relative diminution of both cells and hæmoglobin in the given quantity; conversely, when they clear uric acid out of the blood and produce a diuresis, they will find that the relative quantities of cells and hæmoglobin rapidly return to the position they held before the experiment began.

In my own case, and in the cases of anæmia I have investigated, I have come to believe that I can tell from the concentrated or hydræmic condition of the blood whether there has or has not been a diuresis produced by any drug given.

I look, therefore, upon the fall in specific gravity of the blood of the female which takes place at fifteen as the result of more or less uricacidæmia, which produces in the ways sketched out above both hydræmia and anæmia, and this is itself the result of her very active metabolism at thirteen now coming to an end, and of her menstruation now establishing itself.

As the male is not exposed to these great fluctuations in metabolism with the uricacidæmia they produce, he does not show any corresponding blood changes.

His metabolism goes more steadily ahead, and he lives also, be it observed, at this time of his existence, a much more healthy life than his sister.

I do not believe that there is any "natural tendency," either to a fall in the specific gravity of the blood or to chlorosis; they are simply the results of our meat-eating habits and of our civilisation.

If our girls did not eat so much meat, they would not store so much urate in their time of active metabolism at thirteen, and if at fifteen they led the life of healthy active savages, instead of resting, lying up and becoming semi-invalids, there would be none of the present great fluctuations in their metabolism, but, as in the case of their brothers, their development would go more steadily ahead, there would be no falling urea and acidity, no uricacidæmia, and, consequently, no hydræmia and anæmia.

Further on, Dr. Jones seeks to establish a connection between chlorosis and disturbance of splanchnic innervation with dilatation of gastro-intestinal vessels, and he goes on to say, "This I conceived to be brought about in a reflex manner, and this appeared to me to be the more likely since I had met with some cases in which the usual gastro-intestinal disturbance, together with marked chlorosis, had rapidly followed a shock or chill—generally a shock or chill occurring about a menstrual period." Exactly so, and causing, therefore, a great fluctuation in the excretion of uric acid and the amount passing through the blood. It will not have escaped the notice of my readers that I attribute the effect of menstruation in producing uricacidæmia to a large extent to the gastro-intestinal disturbance it produces, though we have also seen in chapter x. that uric acid itself produces in one way or the other considerable gastro-intestinal trouble.

Before leaving the subject of anæmia, it may be useful to give a short summary of the facts of the case.

First, then, by the clinical observation of paroxysmal hæmoglobinuria and Raynaud's disease, and of splenic leucocythæmia, chlorosis and anæmia, and the relation of many of these troubles to "bilious attacks," dyspepsia and menstruation, I was led to believe that there was an important connection between the blood changes and an excess of uric acid in the blood and urine. As to these facts, I am at one with other observers, but differ from them merely as to their meaning and causation.

Secondly, there is my observation that the value of my blood decimal appears to vary from day to day with the amount of uric acid passing through it, and that if intentional variations are produced in the uric acid, the blood decimal follows suit.

Thirdly, there is my observation that the same holds good for others also, and especially for anæmic and chlorotic patients.

Lastly, we see that the knowledge thus acquired enables us to explain many of the chief points in the causation of these diseases, and will, doubtless, in the future enable us to explain still more.

Before we say anything definite as to the way in which uric acid acts, I think that further observation and experiment are necessary, and I shall here merely point out the bearing of such facts as we have.

First of all, as pointed out above and also in the first edition of this book, it has been shown that the injection of creatinin into the blood stream produces destruction of red cells, and it is possible that uric acid may act in the same way.

On the other hand, uric acid by its effects on the circulation, undoubtedly influences very powerfully the nutrition and the function of such important organs as the skin, the liver, the spleen and the muscles; and I shall have to suggest in the next chapter that it is through its influence on the metabolism in these organs, that it may produce albuminuria and Bright's disease.

I have mentioned above, that one of the blood changes met with in paroxysmal hæmoglobinuria is an increase of coagulability; and several things seem to render it probable that if uric acid thus directly or indirectly, increases the coagulability of the blood, it may exercise an important influence in the pathology of thrombosis.

The frequent clinical connection between thrombosis and gout or diabetes, of both of which I shall have something to say presently, is too well known to need more than mention; and a similar relation is often found between thrombosis and certain post-febrile and puerperal conditions; and after what I have already said about these, I need hardly insist on the fact that one point common to all these diseases, is the frequent presence of considerable excess of uric acid in the blood; then again, unless my clinical observation deceives me, thrombosis is not very uncommon in Bright's disease, and in this disease (as we have seen in chapter iii.) the researches of Professor R. von

Jaksch confirm my own in showing that an excess of uric acid is very frequently to be found in the blood.

From this point of view also I was very greatly interested in Sir J. Fayrer's article on "Intra-vascular Coagulation and Pulmonary Thrombosis" (*British Medical Journal*, vol. ii., 1893, p. 165), for in many of the conditions which he mentions, such as malaria, splenic disease, puerperal conditions, hot, damp weather (see also causation of fatigue, p. 162), and especially surgical operations in hot, damp weather, it seems to me that there is hardly room to doubt that a great excess of uric acid would often be present in the blood.

I shall mention in chapter xiv., the effects of surgical operations in increasing the excretion of uric acid and urea, and I have no doubt that, combined with hot weather, these would greatly increase the quantity of uric acid passing through the blood.

Lastly, there is another point among the symptoms of paroxysmal hæmoglobinuria, of which I am now, I believe, able to give a pretty complete explanation.

It will be readily admitted by other observers, that in the urine of paroxysmal hæmoglobinuria, oxalate crystals are very frequently present; let us enquire further as to their meaning.

In the *British Medical Journal*, vol. i., 1885, p. 167, Dr. Lauder Brunton points out that it has been shown that when sulphuretted hydrogen is allowed to act on a concentrated solution of urates, oxalate of lime is produced; now, in the urine of paroxysmal hæmoglobinuria, we have undoubtedly a concentrated solution of urates, for I have demonstrated both the facts and their causation over and over again; we have probably also sulphuretted hydrogren in this urine, and the point of greatest interest is the way in which this sulphuretted hydrogen is produced.

Dr. Brunton points out that the sulphuretted hydrogen, which produces the oxalate crystals in the urine, is generally formed in the intestines during digestion of cabbages and other food rich in sulphur, and the way in which it comes to be produced in the intestines, in the paroxysm of hæmoglobinuria, is, I think, a point of great interest.

In chapter vii., p. 138, I have pointed out in answer to the arguments of Messrs. Herter and Smith, of New York, on the causation

of epilepsy (*New York Medical Journal*, August and September, 1892), that the intestinal putrefaction of which they noticed so many signs in this disease was the simple and constant result of an excess of uric acid in the blood; and I argued that the excess of urate in the blood which contracted all the arterioles and raised arterial tension to the extent of interfering with the intra-cranial circulation and producing the fits, would interfere also with gastro-intestinal digestion and absorption and allow putrefactive processes to take their place. I doubt not also that a precisely similar explanation may be given of the excess of bacteria in the intestine, and the poison found in the urine as a result of their activity in cases of pernicious anæmia. (See Dr. Hunter, *Lancet*, vol. i., 1891, p. 260.) Here also the uric acid in the blood is the first thing, while the bacteria in the intestines, and any products they may generate, are secondary, and as in the parallel case of epilepsy unimportant. (See also a paper on "Hydrothionuria" in the *New York Medical Journal* of June 17, 1892.) This in many cases accompanied digestive trouble or disease, and it is said that it (sulphuretted hydrogen) may also be formed by bacteria in the urine.

Messrs. Herter and Smith say (previous reference, p. 46 of reprint), "We cannot say why there should occur in epilepsy so considerable a proportion of cases in which there are evidences of excessive intestinal putrefaction." To my mind the explanation seems as simple as it is complete; and I would suggest that a similar explanation can be given of the presence of oxalates in the urine of hæmoglobinuria; for here also we have uricacidæmia and general contraction of arterioles, and while the excess of uric acid is causing the blood destruction, the contracted arterioles suspend gastro-intestinal digestion, and putrefaction, doubtless with the formation of more or less sulphuretted hydrogen, takes its place. A certain amount of that sulphuretted hydrogen passes with the excess of urates in the concentrated urine, and the frequent presence of oxalate crystals in this fluid is thus fully explained. Lastly, the explanation throws backwards a most interesting light on the actual causation of paroxysmal hæmoglobinuria, and demonstrates that it is contemporaneous with the presence of an excess of uric acid in the blood and urine, and deficient circulation in the intestines which we cannot see, as well as in the skin and extremities producing the symptoms of Raynaud's disease, which we can see, and which are well known to be so frequently associated with it.

CHAPTER XIII.

Albuminuria and Bright's Disease.

One of my first papers on the uric acid headache (*Practitioner*, March, 1886) ends as follows:—"And further, as it is by no means uncommon to find in the *post-mortem* room that there are urates in the joints of persons who are not known to have had manifest gout, and that such urate deposits are often associated with granular kidneys, hypertrophied heart, degenerate vessels, and cerebral hæmorrhage, I think that many people who have the forms of headache and the history above described, and are easily affected by butcher's meat, and, indeed, resemble cases of Bright's disease in the manifest benefit they often derive from leaving it off altogether; I think that many of these cases tend to degenerate in this direction as years go on, and perhaps, finally, to enter the *post-mortem* room under some or all of the conditions above mentioned. So that I am inclined to believe that the diet treatment of these forms of headache may mean much more than the alleviation of their pain, and that if it is fortunately begun early in life, it may possibly be the means of preventing, or greatly delaying the more serious and fatal developments."

I believe now much more strongly just what I was beginning to see then, that from the uric acid headache to chronic Bright's disease, the only change is one of degree, and I see no reason to doubt that if I had not altered my diet eleven years ago, I should to-day be suffering from albuminuria.

Since I wrote the lines quoted above, I have seen quite a large number of cases in which periodical sufferers from the uric acid headache have come to suffer from albuminuria and chronic

Bright's disease; and even at this moment I have under my care several cases, of which I shall presently give a few notes, and in which I believe that the transition from migraine to morbus Brightii is occurring before our eyes.

The alteration in my diet has not only prevented my having a headache more than two or three times in a year (in place of forty to fifty times), but it has rendered the attacks in every respect less severe, the coldness of the skin and extremities is much less, the pulse is almost never as slow or of as high tension as it used to be; so that a rate below 60, or tension as high as that shown in fig. 26 is now quite rare, and my general level of pulse tension has, I believe, been lowered to a corresponding extent. Thus the circulation and metabolism in my skin and other important organs has not been hindered to anything like the extent it would have been had I continued my meat diet during these eleven years, and I have so far, therefore, escaped albuminuria and Bright's disease.

Though I never found any in my own case, I believe it is by no means very rare for sufferers from the uric acid headache to have a little albuminuria at the time of the attack or just before it is over; and my experience in this respect is by no means singular; as I notice an article by Dr. Stewart Lockie, in the *British Medical Journal*, vol. i., 1886, p. 1059, on the albuminuria of adolescence and headache as its chief symptom. He also mentions the frequent presence of a gouty family history in these cases.

Then again it will have been gathered from what I said of paroxysmal hæmoglobinuria in chapter xii. that I look upon it simply as a paroxysmal fluctuation in urate excretion, entailing the passage of an excess of uric acid through the blood. It is in fact a severe uric acid storm, and the headache in this case, just as in the cases of albuminuria mentioned above, is very frequently present.

Then also it will be understood that I believe there are to be met with all gradations from the blood changes of anæmia produced by uric acid, to the hetero-albuminæmia (Semmola) and albuminuria, and finally to the hæmoglobinæmia and hæmoglobinuria, of the paroxysmal disease; the factor immediately underlying these blood changes being a deficient circulation in the skin and other important organs of metabolism, and behind this

again, and the cause of all subsequent changes, is an excess of uric acid in the blood.

The contracted arterioles, which raise on the one hand the tension in the arterial system, diminish, on the other hand, the circulation through all the organs and tissues of the body; headache, mental depression and fits, represent, probably as we have seen, the effects of the high arterial tension on the intra-cranial circulation, while arterial degeneration and hypertrophy of the heart are some of its effects on the vascular system; on the other hand, the cold skin and extremities, certain alterations in the skin and other structures up to Raynaud's disease, and the atrophied skin of Bright's disease, and certain changes in the blood, and circulating albumens from anæmia to hetero-albuminæmia and hæmoglobinæmia, represent the effects of the defective circulation in the tissues.

In so far as these changes are due to uric acid, they are at first functional and may be completely recovered from, but when the uric acid storm is severe, and repeated every week for years, the interference with circulation is sufficiently great and prolonged to produce atrophy, and then the full picture of Bright's disease gradually unfolds itself, and complete recovery is no longer possible.

The only course now is to reduce the metabolic needs of the body within the limits which atrophied structures may suffice to perform, just as occurs sometimes in phthisis, when a patient may last for years with only a lung and a half, or less, because the respiratory needs of the body have been correspondingly reduced.

In saying this, it must not be lost sight of that external conditions, such as temperature, will very greatly influence in one way or another the effects of uric acid on the skin circulation; while an internal condition, such as dyspepsia, by keeping up for weeks and months a more or less severe uricacidæmia (see chapter x.), may bring into existence in a comparatively short time, its worst effects on metabolism and nutrition. My clinical observation leads me to believe that chronic Bright's disease, and possibly also the nearly allied condition of myxœdema not very rarely take origin in this way from chronic dyspepsia.

The best proof that uric acid exerts the effect on the vessels, which this pathology postulates, is, I think, to be found in the

fact (previously gone into, chapter v., p. 93) that the urinary water varies from hour to hour, and day to day, inversely as the uric acid excreted along with it, and the further fact that very numerous drugs which diminish the uric acid increase the water, while others which increase the uric acid diminish the water.

As some appear to have misunderstood the bearing of my remarks on the circulation of the kidney (Sewall, *Medical News*, Philadelphia, Sept. 16, 1893), I may perhaps do well to re-state them here.

It is no doubt quite true, as this observer points out, that physiological experiment has shown that the blood supply of the kidney varies directly with arterial blood pressure; but in these experiments the arterioles and capillaries of the kidney remained neutral, whereas my point is that in uricacidæmia the arterioles of the kidney are not neutral, but like the vessels of the skin, the eyes, and the salivary glands, they are more or less strongly contracted; and what I suggested was that this contraction overcame that power of arterial blood pressure to force blood through the kidney, and the remarks I have quoted from Dr. Lauder Brunton (p. 93) show, I think, that this is his opinion.

Clinically I think we meet with scanty urine under two conditions (1) when the heart, being normal, the contraction of arterioles and capillaries is abnormally high, and the kidney circulation is consequently defective; (2) when the contraction of the arterioles and capillaries is not above normal, but the heart is weak or diseased, and has not the power to drive blood through them.

The failure of circulation is, in both cases, due to the fact that the heart has not power to do what is required of it; but a finger on the pulse will enable us in a moment to distinguish between them, for in the first case there will be high arterial tension, in the second almost none. The same argument applies to the circulation in all the tissues of the body, and I have already alluded to it in connection with the incidence of Raynaud's disease on girls and women (p. 225).

This also explains completely the absence of dropsy in chronic Bright's disease, for in this disease the heart at first hypertrophies and works up to its troubles, but when later on, its nutrition with that of the whole body suffers severely, it fails and dilates, and

then retention of water and dropsy quickly supervene, because the arterioles in the kidney and elsewhere get the best of it.

When anything, such as previous pericarditis, prevents the heart from undergoing this conservative hypertrophy, the primary dropsy is marked and persistent, and the end is so rapid that there is no time for chronic changes in the kidney to take place.

Having thus given an outline of the position I have been gradually led to take, with regard to the causation of albuminuria and Bright's disease, I shall now give a little more in detail, some of the facts on which it is founded.

In a paper on "The Connecting-link between the High Tension Pulse and Albuminuria" (*British Medical Journal*, 1890, vol. i., p. 65), I mentioned certain points which seemed to me of interest in connection with the writings of the late Dr. Mahomed and those of Professor Semmola, as bearing upon the causation of the disease, and suggested that hetero-albuminæmia, of which the latter writes and to which the kidney lesions found *post-mortem* are secondary, gave us a good explanation of the causation both of Bright's disease and of so-called functional albuminuria.

I will now mention a few of the points in this paper.

The late Dr. Mahomed pointed out that though a high tension pulse is a common and characteristic feature of Bright's disease, it might nevertheless be present for several years before there is any albuminuria. He said that the high tension and other signs of what he called the pre-albuminuric stage of Bright's disease were probably due to a poison in the blood, and I suggested that many of the signs and symptoms he spoke of were those of uric-acidæmia, and that the poison he was in search of was probably uric acid.

Dr. Mahomed also showed that in certain cases of temporary albuminuria, about which I shall have to speak at greater length presently, the appearance of the albumen was preceded and accompanied by an increase of arterial tension.

I then quoted at considerable length from the works of Professor Semmola, who shows that the appearance of albumen in the urine is due to the presence of an excess of diffusible albumen in the blood (hetero-albuminæmia), the kidney lesions found after death being due to the irritation which this foreign albumen eventually sets up in passing through its glomeruli and tubules.

I pointed out in support of Semmola's thesis that Stokvis in one of his experiments with egg albumen did produce some kidney irritation, resulting in the passage of serum albumen into the urine.

I pointed out that taking Bright's disease as a primary alteration (inflammation) of kidney structure causing serum albuminuria, there is nothing to account for the excess of diffusible albuminoids in the blood as to the existence of which in nephritis the observations of Professor Semmola do not stand alone.

I further said, that while the theory of primary kidney lesion quite failed to account for the clinical symptoms of many cases of so-called "functional" albuminuria, the theory of primary blood lesion (hetero-albuminæmia) might account for them completely.

The chief arguments of Professor Semmola are as follows, and I take them from the work of Dr. Labadie-Lagrave (*Urologie Clinique et Maladies des reins*, Paris, 1888, p. 714, *et seq.*), so as to give my readers the opinions of others, rather than my own, on the work of Professor Semmola.

(1) The amount of albumen in the urine varies with the amount of albumen in the food and not with the renal lesion; therefore the albuminuria is not due to the renal lesion.

(2) The cause of Bright's disease is the action of cold and damp on the skin, but this cold and damp in chronic cases is not able of itself to determine hyperæmia of the kidney; that is to say, the lesion eventually found in the kidney is not the direct result of the action of cold and damp on the skin, therefore there must be some intermediary.

(3) This intermediary is unassimilable albumen; certain portions of the circulating albumens being rendered unassimilable and diffusible by failure in the metabolism of the skin.

(4) This unassimilable albumen is eliminated by the kidneys and other organs, and gradually produces irritation and parenchymatous and interstitial changes in their structure—Bright's disease.

Thus Labadie-Ladgrave says (previous reference, p. 719), "Ainsi donc: accumulation dans le sang d'albuminoides inassimilables: premier fait et consecutivement lesions renales. Tel serait d'apres Semmola l'en chainment du processus dans le mal de Bright."

He then points out that as a result of this doctrine there must be from the very outset a diminution of urea; and that Semmola has long pointed out this diminution, and also the fact that it is due to diminished formation as the amount of urea in the blood in early Bright's disease is less than in healthy blood, so that there is no accumulation, nor is there any increase of creatin, creatinin, or other intermediate nitrogenous products.

I have also pointed out in chapter iv., p. 85, the way in which uricacidæmia by interfering with the circulation in the liver, muscles, skin, &c., may hinder metabolism, and lessen the formation of urea.

But this theory of hetero-albuminæmia is no mere hypothesis, for Semmola bleeds his patients, and demonstrates that their blood contains excess of albumens that diffuse; also that blood which contains this excess will produce albuminuria when injected into a dog, and this albuminuria will be proportional to the amount of diffusible albumen in the blood injected.

Labadie-Lagrave (previous reference, p. 727) further points out that Semmola has shown that in Bright's disease there is not only anæmia of the skin, but that its glands, epithelium, and cells of the Malpighian layers have undergone most extensive atrophy, this doubtless carrying with it great interference with function and healthy metabolism; while in albuminuria due to other causes, as morbus cordis, alcholism, gout, there is no alteration whatever in the structure of the skin, and he concludes his notice as follows:—"Telles sont les derniers recherchés toutes recentes du professeur Semmola, qui viennent si brillamment a l'appui de la theorie dont il est l'ardent défenseur" (p. 728.)

On this theory an albuminuria is on all fours with a glycosuria. No alteration of kidney structure has been suggested to account for the latter. On the contrary, it is known that any excess of sugar in the blood at once passes off by the kidney, and that this sometimes causes hyperæmia and irritation of the kidney. On Semmola's theory albuminuria is due to excess of diffusible albumen in the blood, and this, in its passage through the kidney, causes more severe irritation and nephritis.

Lastly, I pointed out that uric acid (the poison of which Mahomed noted the effects, and which I identified from the clinical symptoms it produced) might bring about hetero-albuminæmia, with secondary albuminuria and nephritis, and thus

form the connecting link between Mahomed's observations on the high tension pulse of the pre-albuminuric stage and actual Bright's disease.

I suggested that uric acid by contracting the arterioles (as it does when it raises the tension) might interfere seriously with the metabolism of albuminoids both in the liver and the skin (which accords with Semmola's facts as to the causation of hetero-albuminæmia) and that when this action is very intense we might get breaking up of hæmoglobin itself as in paroxysmal hæmoglobinuria (the most intense condition of hetero-albuminæmia), the symptoms accompanying which I pointed out are just those of a uric acid storm (uricacidæmia). (See p. 230.)

On the other hand, I pointed out that the violent action of uric acid on the capillaries and arterioles might account for that disease which is most nearly related to paroxysmal hæmoglobinuria, and like it is accompanied by marked clinical signs of uricacidæmia, namely, Raynaud's disease; and that the symptoms of the pre-albuminuric stage according to Dr. Mahomed, are cold hands and feet, imperfect digestion, bronchitis, gastric catarrh, headache (especially hemi-cranial), loss of memory, depression, weariness, cloudiness of intellect and hypochondriasis, and after what I have said in previous chapters as to the causation of these symptoms by uric acid I must leave my readers to judge of their meaning.

It seems then that at this point we have three chief theories as to the causation of albuminuria :—

(1) That it is due to heart failure (which applies, I suppose, only to temporary albuminuria and not to Bright's disease).

(2) That it is due to irritation of the kidney by a poison in the blood (Mahomed).

(3) That it is due to hetero-albuminæmia, just as glycosuria is due to glycæmia, and that irritation and structural change in the kidney are secondary (Semmola).

And to this last I have added the suggestion that, while hetero-albuminæmia may be due to the action of cold on the skin, the contraction of vessels which uric acid produces may bring about very similar effects, or at least greatly increase the power of cold.

Then in the *Guy's Hospital Reports* of 1881, we find Dr. Mahomed speaking of cases of nephritis, and also of convales-

cence from scarlatina, in which there is no albumen while they are in bed; but it occurs on getting up and going out; and with reference to this he says (p. 416), "The rapidity of the change is too great for the kidney condition, determining it to be a structural one; it must be functional, or more probably a vascular phenomenon. The fact stands, therefore, that the same kidney, and that a diseased one, can produce alike normal and albuminous urine." This observation, it will be noted, is in complete accord with that of Semmola quoted above, that the albuminuria does not correspond with the kidney lesion.

I do not deny that certain vascular conditions can produce albuminuria (notably congestion in severe morbus cordis), but I do deny that cardiac weakness and congestion accounts for the albuminuria in the cases of so-called functional albuminuria mentioned in my paper in the *British Medical Journal*, January, 1890, p. 65, or for temporary albuminuria in cases of chronic Bright's disease such as those spoken of by Dr. Mahomed.

I also deny that uric acid in the blood directly irritates the kidney and produces albuminuria and eventually nephritis, though I have no doubt that an accumulation of urates, or for that matter of pigment or other matters in the kidney, or even the mere passage through it of sugar or bile, cantharides, &c., may produce congestion and slight albuminuria, but that is in many ways a very different matter from nephritis. Urates also may accumulate to a large extent in the kidney just as they do in the joints and other fibrous tissues—"gouty kidney"—but this also is probably a different thing from parenchymatous and interstitial nephritis.

As to heart failure, there is no doubt that this may produce congestion of the kidney and albuminuria. Semmola himself admits this, but he points out that when albuminuria is due to this cause the blood does not contain any excess of diffusible albumen, which at once distinguishes cardiac cases from those of Bright's disease; and cardiac kidneys are generally easily differentiated from those of Bright's disease *post-mortem*.

In transitory albuminurias in apparently healthy subjects not due to mechanical causes, in albuminuria in the course of *maladies dicrasiques* and in the albuminuria of convalescence from scarlet fever, Semmola finds excess of diffusible albumen in the blood—an excess which is proportional to the amount of albumen that is eliminated in the urine.

Mahomed's theory regarding the local irritation in the kidney produced by his hypothetical poison as the cause of albuminuria and Bright's disease fails to explain two points of great importance in that disease: (1) Semmola's excess of diffusible albumen in the blood, and (2) the diminished output of urea which is generally acknowledged to accompany or even precede the onset of Bright's disease.

As Semmola remarks, his hetero-albuminæmia gives the best possible explanation of the diminished urea, for if albumen is not metabolised but excreted unaltered, the formation of urea must obviously be reduced.

I would also remind my readers again that in all uricacidæmia there is a diminished formation and excretion of urea, and that from my point of view chronic uricacidæmia is equivalent to the pre-albuminuric stage of Mahomed, and leads inevitably to chronic Bright's disease, so that I can easily account for the diminished urea.

But if these theories fail, let us see how far the theory of hetero-albuminæmia will carry us in explaining the history and symptoms of Bright's disease.

Semmola says that anything that interferes with the functions of the liver or the skin may hinder the proper metabolism of albumens and produce hetero-albuminæmia, which he regards as the first stage in the causation of albuminuria and nephritis.

I have suggested that uric acid, by its action on the arterioles and capillaries may interfere in the way sketched out above with the functions of the liver, and by contracting its arterioles, as it clearly does during an attack of uric acid headache, may also seriously interfere with the functions of the skin; hence, in accordance with Semmola's reasoning, it may produce hetero-albuminæmia and albuminuria. (See also chapter iv.)

I pointed out in my paper on albuminuria (previous reference) that the theory of heart failure would not explain the cases described by Dr. Dukes (*British Medical Journal*, vol. i., 1889) in which, in association with high tension pulse, there was albuminuria when the patients were up and about, except when they were on milk diet; but no albuminuria when they were in bed, no matter what diet they were given. These cases differ from those of Mahomed previously mentioned in that another factor in causation (namely, diet) is introduced. Mahomed's cases might have been due to

heart failure, because the albumen appeared when they were up and out and disappeared when they were in bed; but in Dr. Dukes' cases the patients might be up and about, and yet have no albuminuria so long as they kept to milk diet, and it appears to me to be nonsense to say that the heart failed on ordinary diet, but did not fail on milk. Hetero-albuminæmia, however, will explain these cases easily, for milk is, according to Semmola, the form of albumen which requires least elaboration by the skin, and I have suggested that this is due to the fact that it is really the product of a skin gland; then again, they have no albuminuria while in bed no matter what diet is taken, because the warmth of the blankets relaxes the vessels of the skin and counteracts the effects of uric acid.

I have also spoken of the albuminuria that sometimes follows a cold bath, and have suggested that it is due to hetero-albuminæmia following the contraction of the vessels of the skin by cold, more or less aided by uric acid, which is generally in excess in the urine and blood in the morning hours; heart failure, again, seems to me an inadequate explanation, as the heart has just had the benefit of a night's rest and recuperation.

Again, in Dr. Dukes' cases the albumen is excreted in greater quantity after meals, especially after breakfast, than at other times of the day. Why should the heart fail in the morning after breakfast more than at any other time?

In a more recent paper (*Lancet*, vol. ii., 1891, p. 1327) Dr. Dukes attributes to more or less chronic congestion of the kidney the albuminuria of adolescents, and the Bright's disease into which he thinks it may eventually develop; but as I have before remarked a congestion of the kidney will not explain an excess of diffusible albumen in the blood or a diminished formation of urea.

My explanation of Dr. Dukes' cases is uricacidæmia producing contracted vessels and high tension, hampering the functions of the liver or skin, or both, producing hetero-albuminæmia and albuminuria; and the albuminuria is most marked at those hours at which, in the natural physiological cycle, the uricacidæmia is most intense, the pulse slowest, and the urinary water lowest. Dr. Saundby points out ("Lectures on Bright's Disease," p. 15) that in Bright's disease also the albuminuria is greatest after meals, and especially after breakfast, and in the one or two

instances in which I have been able to examine the point this has certainly been the case; so that these "functional" cases resemble, in this respect at least, the organic disease, and I for one am quite ready to believe that they may pass into it.

Now let us look at the etiology of acute Bright's disease. Sir W. Roberts says ("Urinary and Renal Diseases," ed. iv., p. 471): "That complex of impressions, which is familiarly known as taking cold, is the common cause of Bright's disease in its acute form;" and in common with other writers he mentions also scarlatina and alcohol.

Now I hope that after what I have said in previous chapters it is unnecessary again to point out the way in which all these factors act in producing a fluctuation in the excretion of uric acid, the fluctuation resulting in the production of more or less severe uricacidæmia which brings about, we are supposing, hetero-albuminæmia, albuminuria, and nephritis.

I do not deny that high tension and contracted arterioles, which interfere with the circulation in the kidney and produce scanty urine, do probably, to some extent, also interfere with its nutrition, and that where such high tension is very frequently present the interference with nutrition may be carried to the extent of producing structural change; but granting all this we are no nearer to an explanation of Semmola's facts—the excess of diffusible albumen in the blood, and the diminished formation of urea in Bright's disease.

I am obliged at present to take for granted that they are facts, and I believe that they have been tested by others, and that in so far as they have been called in question Semmola has been very well able to take care of himself, and give a complete and satisfactory explanation of differing results. Thus in *Le Bulletin de l'Academie de Medicine*, Paris, July, 1890, M. Hayem remarks that the transfusion of the blood of a dog suffering from advanced Bright's disease into the vessels of a healthy dog produced no albuminuria. In reply, Semmola says that there was no proof that there was much diffusible albumen in the blood injected; and the mere fact that an animal has advanced Bright's disease does not show that it has much hetero-albuminæmia, though hetero-albuminæmia was the original cause of the nephritis.

I should have myself repeated all these experiments several years ago but for the great difficulty that exists in this country in

obtaining a few ounces of blood on which to work; but I believe that the main points have been accepted by Vulpian (see Saundby, previous reference, p. 12), Labadie-Lagrave and others, and I shall certainly not lose an opportunity of testing the diffusibility of the albumens of the blood in Bright's disease when it offers itself.

Possibly Bright's disease, especially the chronic form, is a product of two forces, (1) the effect of contracted arterioles on the nutrition of the kidney, and (2) the irritant effect of hetero-albuminæmia and the passage of a foreign albumen.

Cold raises acidity, fever raises acidity, most alcoholic drinks raise the acidity, and these last, acting over long years, hold back and retain in the body large quantities of urate which provides the material for eventual chronic and severe uricacidæmia in old age or other failure of nutrition; and this uricacidæmia is to my mind the cause of the chronic nephritis so often found in the *post-mortem* room with chronic gout. (See Dr. Norman Moore, *St. Bartholomew's Hospital Reports*, vol. xxiii., p. 289.) Further, the excess of urates which under these conditions passes into the blood and out in the urine, is the cause of the gravel and calculus so frequently met with in the declining years of life. (Compare also case mentioned on p. 23.)

But where the uricacidæmia is more sudden and severe as when it results from sudden severe chill (a case under my care got his disease by being called from the stoke-hole of a steamer to stand twelve hours or more on deck, where he got wet through in five minutes and had to remain so), it may produce not only hetero-albuminæmia; but the urate may, as I have suggested, acting in sequence to the chill, attack also the red cells and cause hæmoglobinæmia and hæmoglobinuria, and it appears that in some cases paroxysmal hæmoglobinuria has formed the starting point of acute Bright's disease. (*Lancet*, vol. ii., 1889, p. 1007).

With regard to the causation of paroxysmal hæmoglobinuria, Sir W. Roberts says (*loc. cit.*, p. 162): "Most observers are now agreed that the solution of hæmoglobin in the serum precedes its appearance in the urine, and that the symptoms of kidney affection which are sometimes present are due to the irritation produced by the passage of the hæmoglobin through these organs."

Here, then, in the case of paroxysmal hæmoglobinuria the whole of Semmola's contention is quietly admitted: first of all

that the escape of the blood constituents in the urine is due to their breaking up in the circulation itself, and second, that their passage through the kidney causes irritation in that organ.

If it is granted that in place of such violent and temporary destruction of blood elements we may have severe hetero-albuminæmia lasting continuously over several days (less intense, but of longer duration), may we not see in this the causation of acute Bright's disease as it is met with clinically? and there is no difficulty in granting this, as numerous observers (notably Dr. Stephen Mackenzie, *Lancet*, vol. i., 1884, p. 243) have seen albuminuria both preceding and following the hæmoglobinuria.

The following case throws, I think, some light on the causation of albuminuria in the way I am suggesting, by the action of cold or uric acid or both on the vessels of the great metabolic tissues.

E. H., age 44, a patient of Dr. Tomson, of Luton, Beds., to whom I am indebted for the history of the attacks.

Complains of attacks of "liver" every three months or oftener, accompanied by extreme mental depression, shivering and retching, and followed by rise of temperature. Subject to these attacks as long as he can remember.

Had fits at 5 and 12 years of age.

His mother died of phthisis at the age of 50.

His father is still alive and well, aged 83.

Two brothers (one an imbecile) and one sister died of phthisis.

One sister has functional twitching and contractions of the muscles of both arms.

Other members of the family exhibit evidences of an insane neurosis.

Patient was operated on for anal fistula in 1892.

The following is Dr. Tomson's account of an attack he saw in December, 1892.

"Condition distinctly hysterical; throws himself about on the couch, and repeatedly cries out 'Oh, I'm so bad! Oh, I'm so bad!' A constant restlessness. He shivers, and the teeth chatter; occasional retching, but nothing brought up; pulse 108; artery contracted, high tension, temperature just under 100°, liver much enlarged three fingers' breadth below the ribs. Urine high coloured; no albumen.

"In this condition he remains for two or three days and then

gets better. The more noticeable features are the rapid enlargement of the liver, and its equally rapid subsidence at the termination of the seizure, and the intense misery of the patient." He has severe attacks like this about every three months, and less severe attacks between times.

When I saw him he told me that he had had a headache on the previous day, which began at 11.30 a.m.

His pulse was only 54, and both to finger and sphygmograph showed extremely high tension; the first sound of the heart was prolonged or reduplicated between the apex beat and the sternum, and the second sound was loud; he had thus both the cardiac and arterial signs of high tension (p. 113). The liver dulness was not enlarged, and its edge could not be felt; and now we come to a point of very great interest. The urine which he passed here (12 noon) was high coloured and specific gravity 1020, contained a large quantity of albumen, 4 per 1000 (Esbach), and no sugar. Under the microscope it showed numerous oxalate crystals, and a few casts hyaline and slightly granular. This was the first time albumen had been noticed in his urine.

Let us try to group these symptoms and estimate their meaning. *Contracted arterioles and high arterial tension* shown in the attack described by Dr. Tomson, in the condition of the pulse, the shivering and teeth chattering, the high coloured and probably scanty urine. The hysterical conditions, and the mental depression are the effects of the high arterial tension on the intra-cranial circulation, just as the shivering may be the effect of the deficient circulation in the skin: I have myself had just such shivering or slight rigors in my attacks of uric acid headache when they used to be severe.

What is the meaning of the marked enlargement of the liver? I would suggest that it is a venous congestion or hyperæmia due to failure of the heart before the high arterial tension; when I saw this patient there was very high tension, but the pulse rate was only 54; there was therefore no sign of heart failure, and with this there was no enlargement of the liver; but in the attack described by Dr. Tomson the pulse rate was 108, and yet he says the tension was high; now such a pulse rate with high tension almost certainly means heart failure, and it is possible that the vessels of the lungs were at the same time greatly contracted (see chapter ix.), and that this told specially on the right heart and the liver.

What was the cause of the high arterial tension? Excess of uric acid in the blood; the urine was high coloured and probably scanty, and we know that the urinary water is inversely as the uric acid excreted along with it; therefore there was excess of uric acid in the urine and probably also in the blood. I look upon these so-called "liver" attacks then as uric acid storms almost if not quite identical with my attacks of uric acid headache, and in these attacks in myself I have often noticed some distinct evidence of more or less temporary congestion of the liver, such as pain, weight, fulness, or a feeling of heat or tension in the right hypochondrium, and these sensations are at their worst when the arterial tension is greatest, and I now rarely or never suffer from them.

Now we come to the trouble at the time I saw him; again the signs of contracted arterioles and a high tension are most marked in the heart and arteries, there was a headache no doubt the result of this tension the previous day, and the urine is found to contain a lot of albumen together with some casts and some oxalates, the urine was free from albumen a day or two before and it became again free from albumen a day or two later.

We have, then, here almost complete the picture, not of paroxysmal hæmoglobinuria, but of the next thing to it, paroxysma albuminuria.

Now the point on which the whole of this chapter hinges, is the way in which this albuminuria was produced; let us look closely at the meaning of the symptoms accompanying it.

A urine of high colour and specific gravity, and therefore almost undoubtedly containing some excess of uric acid. Again, we have seen in the previous chapter that oxalates may mean the simultaneous excretion of intestinal putrefactive products (sulphuretted hydrogen) with an excess of urates; so that here again we have independent evidence that an excess of urates was excreted in this urine, but why was there intestinal putrefaction? Because the vessels of the intestines like all the vessels in the body were contracted by uric acid, the very uric acid which was passing in excess in the urine. Again we know that the vessels were contracted on the day before the albuminuria, because high arterial tension was the probable cause of the headache from which the patient told us that he suffered.

We have, then, some very strong evidence of the presence of

high arterial tension and contracted arterioles and capillaries, and evidence that these had been present for at least twenty-four hours before I saw the patient and found albuminuria. We have also some very good evidence that these arterioles and capillaries were contracted, owing to the presence of an excess of uric acid in the blood.

We have seen also in previous chapters that excess of uric acid in the blood, may not only account for the blood changes of anæmia, but also for those of paroxysmal hæmoglobinuria, and we know that albuminuria may both precede and follow hæmoglobinuria, so that it is extremely probable that hæmoglobinæmia and hæmoglobinuria are but more advanced stages of hetero-albuminæmia and albuminuria.

I am suggesting, then, that the chain of causation in the case of this albuminuria was as follows: a uric acid storm or fluctuation of excretion resulting in uricacidæmia, general contraction of arterioles and capillaries, deficient circulation in the skin, liver, intestines, and other organs of metabolism; as a result of this retrograde changes in the albumens of the blood and tissue fluids (hetero-albuminæmia of Semmola), which in some cases may go on to hæmoglobinæmia; but in this case stopped short at hetero-albuminæmia and albuminuria.

Some may say "You spoke of congestion of the liver just now; why may not a congestion of the kidneys similarly produced account for the albuminuria?"

First of all, at the time of this albuminuria, there was no evidence of congestion of the liver, and again even if we grant that there was congestion of the kidneys that would not account for all the conditions; suppose that instead of stopping short at albuminuria, the attack had gone on to hæmoglobinuria, ow could any congestion of the kidneys account for the destruction of a million red cells in the blood stream itself?

No congestion of the kidneys can account either for hæmoglobinæmia or the hetero-albuminæmia of Semmola; any such explanation therefore falls to the ground.

Taking the view, then, that this patient's troubles were of the nature of paroxysmal albuminuria, and due to recurrent uric acid storms, the obvious indication was to reduce the uric acid income and formation, I accordingly suggested a considerable reduction in the amount of meat and animal food, and I believe he went

beyond my suggestions and became almost a vegetarian. In the six months that have elapsed since this change of diet he has had no attack of "liver," no albuminuria, and is in many other respects much better.

The time is too short to allow of any final judgment as to the results of treatment, but so far it seems to have had the very same effect that it had in my own case—with the removal of the cause the effect has disappeared.

And this is another point on which I wish to lay special stress, namely, that when the diagnosis of uric acid disease has been well and properly made, treatment of the uric acid should without fail effect a cure.

On the other hand, an intentional increase of the uric acid should equally without fail make all the symptoms worse.

Further, it is a distinguishing mark of these metabolic albuminurias that they are greatly influenced by diet, that, as pointed out by Semmola and others, the amount of albumen excreted is to a considerable extent proportional to the amount ingested, and that by reducing this amount and, further, by taking it in a form which is easily assimilated (milk, Semmola), these albuminurias so long as they remain functional can be greatly reduced or cured; and the experiences of Dr. Dukes quoted above confirm what I am saying.

Supposing, on the other hand, that nothing is done and the patient continues to form and take in large quantities of uric acid, not only will his attacks continue, but they will get more and more severe as he gets older; for the slackening metabolism which comes with age will favour the passage of a larger and larger excess of uric acid through the blood, and thus the metabolic albuminuria, which was at first paroxysmal and functional, will become organic owing to wasting of the metabolic tissues, structural changes will take place in the kidney owing to the constant irritation of hetero-albuminæmia, and so we gradually pass from a mere uric acid storm to fully developed morbus Brightii, and I have seen, as I say, quite a number of cases in which periodical sufferers have found their attacks getting more frequent and severe, and have then, on examination for insurance or other cause, discovered both albumen and casts in their urine; and such cases are very fortunate if treatment of the uricacidæmia relieves and removes all their troubles.

On the other hand, I have seen quite a number of cases of albuminuria, either temporary or intermittent, when diet treatment has almost at once removed the albuminuria and many of its concomitant symptoms, and the cure has appeared to be permanent.

Some evidence in favour of Semmola's theory of hetero-albuminæmia is given by the late Dr. Cranstown Charles in a paper on "Intermittent Albuminuria" (*St. Thomas's Hospital Reports*, vol. xxi.), and he mentions that in one young man he found, just as Semmola had done, some albumen in the perspiration and saliva, as well as in the urine.

The same author mentions several interesting cases of albuminuria associated with high arterial tension, mental depression or headache; one case in which there was albuminuria at the menstrual periods, and another case in which it was associated with constipation and relieved by blue pill and salines. I should have no doubt that the mercury and the salines affected the arterioles and capillaries as well as the intestines. He also speaks of the effects of exposure to cold and its possible influence on the skin, and mentions several other points which are in favour of the metabolic origin of these albuminurias.

I have already said that the cases of albuminuria described by Dr. Dukes are associated with high arterial tension, influenced greatly by diet, and that he himself considers that they often pass on into Bright's disease.

I differ from him, however, in believing that such albuminuria and such Bright's disease are not due to hyperæmia of the kidneys, but the result of a failure in metabolism and hetero-albuminæmia, which alone will explain all the facts of the case.

When the failure of metabolism is slight and the hetero-albuminæmia occasional, very slight change in diet, clothing, exercise, or climate, may suffice to remove it, as in some of the cases I have mentioned; but when it is more severe, and especially when owing to atrophy of metabolic structures it has become organic, or still more, if it is complicated by a kidney lesion, these measures will no longer remove the albumen, and complete cure may be impossible.

The kind of albumen excreted seems also to tell the same tale, for it is now pretty generally recognised that in functional cases as well as in paroxysmal hæmoglobinuria, the albumen in the urine is mostly globulin, which dialyses freely, while in advanced

cases with probably distinct and definite kidney lesion, serum albumen is present, which will not dialyse. (*Lancet*, vol. ii., 1889, p. 1086.) Now Professor Semmola pointed out many years ago that in early and acute cases there is an excess of diffusible albumen in the urine and in the blood; while in advanced cases with distinct kidney lesion, the albumen in the urine may be almost entirely serum albumen.

The serum albumen passes only when there is a kidney lesion; the diffusible albumen passes at any time, because it is diffusible. Its presence in the urine is a sign of hetero-albuminæmia, just as glycosuria is a sign of glycæmia.

Where diffusible albumen is alone present, the conditions are still functional, and diet treatment which removes the hetero-albuminæmia, may cure quickly and completely; but where serum albumen is passing, diet will no longer cure promptly, and may not cure at all, for the removal of the hetero-albuminæmia does not do away with the kidney lesion which is now present and allows the serum albumen to pass.

It has been pointed out, that pyrogallic acid, toluylendiamin, &c., when used to produce hæmoglobinuria in animals do eventually bring about severe nephritis. (*Lancet*, vol. i., 1885, p. 115.)

Is it the substance itself, or its effects on the blood, that produce the nephritis? Semmola, at least, would probably attribute a share of the result to hetero-albuminæmia and hæmoglobinæmia. Dr. Ralfe suggests (*Lancet*, ii., 1886, p. 764) that functional albuminuria is but a minor degree of paroxysmal hæmoglobinuria; and I have pointed out that in both troubles there are often abundant signs and symptoms of uricacidæmia; and this author himself points out, that in functional albuminuria there are frequently bilious attacks which I should translate by the one word uricacidæmia. (See p. 270.) He also says that arsenic diminishes the hæmolytic action of the liver, and strengthens the resisting power of the red cells; it did not appear to do so in the case of Daniel H. given above (p. 232); but there was severe uricacidæmia, and treatment of this was followed by general improvement. Several writers have suggested that bile salts affect the hæmoglobin. (MacMunn, *British Medical Journal*, vol. ii., 1888, p. 117; Oliver, *Lancet*, vol. i., 1885, p. 977.) They may do so, but it seems to me that the known effects of uric acid give a better explanation of concomitant symptoms, and in many cases, as I have shown, there is evidence of uricacidæmia.

But supposing that uric acid in the blood can thus bring about hetero-albuminæmia, albuminuria, and nephritis; the nephritis, when it has come into existence, will have an important effect on the excretion of uric acid; for anything in the nature of inflammation in the kidney must diminish its alkalinity; and if the alkalinity of the kidney is less than that of the blood and tissue fluids generally, it follows from my first principles (chapters ii. and iii.) that any uric acid that comes to the kidney will be rendered insoluble and retained, instead of being excreted, hence it comes about that though we have plenty (too much) of uric acid in the blood, we have too little in the urine in Bright's disease.

Hence it comes about that in acute nephritis (but not so much in very chronic disease), no matter what may be the alkalinity of the blood, we get a holding back and retention of uric acid in the body, because the diminished alkalinity of the kidney is unfavourable to its solubility and excretion.

Hence, in nephritis we have chronic uricacidæmia and its signs, contracted arterioles, high tension pulse, if the heart is a strong one, slow action of heart (bradycardia), scanty urine, retention of water in the body and general dropsy, with other signs of uricacidæmia, such as headache, mental depression, tendency to suicide, all of which are well-known to occur in Bright's disease.

An interesting case, illustrating some of these points, was admitted under the care of my colleague, Dr. Tooth, at the Metropolitan Hospital, and he very kindly gave me leave to mention it. A boy, 8 or 9 years old, admitted with subacute nephritis and general dropsy. Urine only 15 to 16 ozs., in twenty-four hours. Measles was accidentally introduced into the children's ward, and this patient, with others, took the disease. The effect was magical. As soon as the fever had reduced the tension, the urine ran up, and was for several days, about 80 ozs. in the twenty-four hours, and in two or three days the dropsy had nearly all gone. Here the rise of temperature and concomitant rise of acidity cleared the blood of uric acid, relaxed the arterioles, among others those of the kidney; the result was a copious diuresis and removal of the dropsy.[1] Now, precisely the same

[1] In myself the first rise of temperature runs the urine up from about 50 cc. an hour to, say, 150 in the same time, and this continues for 4 to 6 hours; but then the supply of water is exhausted, and for the next 24 to 36 hours the blood

can be done with drugs, acids, opium, mercury, any of those in chapter ii., mentioned as causing retention of uric acid, and the result will be proportional to their power over uric acid. In some cases of nephritis I have, with these drugs, altered the pulse rate from about 44 to 80 or above (see fig. 24, p. 104) at the same time reducing its tension, and with this went increase of urinary water, removal of dropsy, and diminution of albumen. Nature is, however, generally more powerful than any drugs, as the above case well illustrates; but I believe that she acts in the same way by clearing the blood of uric acid.

It may be asked, why, in chronic interstitial nephritis, while there is still great arterial tension, do you get no holding back of water, and no dropsy?

I have suggested, as the result of my own observations on the matter, that in chronic nephritis the uricacidæmia is greater in the alkaline tide of the morning, and, as a result, the pulse is slower, and the urine more scanty at this time. Later in the day —the evening and night—uricacidæmia is less, the arterioles are relatively relaxed, and a considerable diuresis makes up for the scanty excretion of the other hours. (See quantities of urine per hour in table given by Saundby, previous reference, p. 15.)

For a case in which this was so, see *Lancet*, vol. ii., 1893, p. 133. In this way there is no retention of water in the body in chronic Bright's disease, for though the arterioles are contracted, and the tension high, the heart is equal to its work, and especially at night the circulation is free. In acute Bright's disease, the sudden contraction of arterioles may overpower the heart, and dropsy results. In all cases I believe it is a struggle between the heart and the arterioles; if the heart fails there is dropsy, if it wins there is none. (See Marey's observations, quoted in chapter v., p. 92.)

In chronic nephritis, also, the alkalinity of the kidney is less reduced than in the acute disease, hence the holding back of uric acid and consequent uricacidæmia is relatively less severe.

Uricacidæmia is probably, therefore, more severe in sudden and acute cases, and this corresponds with the relation of uræmia, the poison of which is, I believe, in not a few cases, simply uric

is very concentrated and the urine scanty. The extent and duration of the diuresis thus obviously depend on the quantity of fluid available, and it is only where there is dropsy, as in the above case, that it can last very long.

acid, and its symptoms, at least the most prominent ones, are the results of the action of this poison on the vessels, and so on the circulation of the brain.

Before the attack, as is well known, the urine is often extremely scanty and the pulse may be as slow as 40 (intense uricacidæmia). The case in which I altered the pulse rate from 44 to upwards of 80 had slight convulsions, severe headache and other signs of uræmia at the time of admission under my care.

The very close parallel between the symptoms of uric-acidæmia and those of uræmia has long interested me, and I believe that till a fatal lesion is produced, I have the same power over the one as the other. Let us look for a moment at the main symptoms of uræmia, and first, epileptiform convulsions. I have shown that similar convulsions may be the work of uric acid; then headache, giddiness, drowsiness, cold skin and cold sweats, local arterial spasms, "dead hand," vomiting, slow high tension pulse, scanty urine—why, these are all the signs of the uric acid headache (migraine). Amaurosis, again, is probably merely an exaggeration of the well-known eye symptoms of migraine, and the contraction of arterioles in the retina pointed out by Morton and others (see p. 112 and 124) as occurring in migraine.

We have here, then, as I have shown, all the causes which produce uricacidæmia; and all the signs of its presence and, further, all the drugs which do good in treatment (opium, acids, &c.), clear the blood of uric acid, while bleeding mechanically reduces the tension and pressure by means of which the uric acid fatally affects the nerve centres. (See p. 123.) I therefore regard dropsy as for the most part due to retention of water in the body, owing to contraction of the renal arterioles and capillaries by uric acid: and when under these conditions, the urine is scanty, the blood will be found to get more and more watery, both the cells and hæmoglobin being relatively reduced; and this fact alone is sufficient to prove that the scanty urine, either in physiological or pathological conditions, is not due to want of water in the blood and tissue fluids. In the same way I regard the cerebral symptoms of uræmia as due to the increase of intra-cranial pressure, which again is partly due to the high arterial tension, and partly to the increase of cerebro-spinal fluid which the high arterial tension causes (p. 124).

In a case under my care, a patient suffering from chronic

arthritis and periostitis (believed by Mr. Walsham, who saw him with me, to be rheumatic), and also from parenchymatous nephritis, I was interested to find that both troubles fluctuated together; that when he had increased trouble in his joint he also had increase of albumen or even recurrence of blood in his urine, so that it looked almost as if the condition (? rise of acidity) which drove the uric acid into and produced increased irritation of his joint, had driven some also into the kidney (gout of the kidney) and increased the renal trouble, and I think we must not altogether lose sight of this possibility; but, on the other hand, it is clear that any arthritis which is due to uric acid, is due to a fluctuation of uric acid—that is, there is first an excess of uric acid in the blood (uricacidæmia) and then some rise of acidity precipitates it on the joint (see chapters xv. and xvi.), and though both troubles appeared to get worse together the increase of albumen may have been due to the uricacidæmia in the way I have suggested and not to the local irritant action of uric acid in the kidney.

I was greatly interested in this case because, when I put him on a lowly nitrogenous diet, both his arthritis and nephritis steadily improved together, and he was greatly pleased with the results of this treatment. I have no doubt that both were due to uric acid, the action being direct in the arthritis, probably indirect in the nephritis.

Let us for a moment revise the facts quite apart from any theory.

Bright's disease is commonly associated with a slow pulse of high tension. Von Jaksch has shown that there is often excess of uric acid in the blood in Bright's disease. I have shown that excess of uric acid in the blood produces, in accordance with Marey's law, a slow pulse of high tension. I have also shown that I can influence, to a very considerable extent, the rate and tension of the pulse, both in physiological conditions and in Bright's disease, by drugs which affect uric acid. That all drugs which affect uric acid, in the same way produce the same or similar results, and that the result is proportional to their effects on uric acid.

Mahomed showed that a poison in the blood was the first step in Bright's disease, and he described the symptoms of this condition (pre-albuminuric stage).

I have shown that these symptoms correspond in every way with the work of uric acid, and that the main symptoms of uræmia are probably merely exaggerations of these.

Semmola has shown that the first stage of Bright's disease is contemporaneous with a diminished formation of urea and an increased diffusibility of the albumens circulating in the blood; and that the kidney lesion is secondary, being due in acute cases to congestion, plus the irritation of the continued passage of a foreign albumen; in more chronic cases to the latter alone, and that the albuminuria is proportional to the blood lesion and not to the kidney lesion, as you may have much albuminuria without kidney lesion, and, on the other hand, much disease of the kidney without albuminuria, as is well known and often observed in chronic nephritis.

I have shown that excess of uric acid in the blood diminishes the excretion of urea, and that drugs which clear uric acid out of the blood commonly increase at the same time the excretion of urea.

And now for theory to string these facts together. Semmola attributes the fall in urea formation to the incomplete combustion of certain albumens, and this incomplete combustion is due to failure in the functions of the liver and skin, the latter of which he has shown undergoes a considerable amount of atrophy in Bright's disease.

Then I have suggested that uric acid might be the poison, the existence of which Mahomed suspected; that it might account for all the symptoms of the pre-albuminuric stage, as he described them; and further, by interfering with the circulation in the muscles, the liver, the skin, and the kidneys, an excess of uric acid (uricacidæmia) might actually produce the excessive diffusibility of albumens (hetero-albuminæmia) and the secondary fall in the formation of urea (see p. 112); thus forming the "connecting link" between the "pre-albuminuric stage" of Mahomed, and the actual onset of Bright's disease; that the kidney irritation would further prevent the excretion of urate, and bring about severe and prolonged uricacidæmia, which, by still further hampering the liver, the skin, and the kidneys, might bring about structural change, and eventually atrophy and degeneration in all three, as met with in advanced Bright's disease.

I may also point out briefly that this theory explains nearly every fact of importance in the treatment of Bright's disease.

In acute disease, the treatment which Sir W. Roberts favours, that by carbonate and citrate of potash, facilitates the excretion and elimination of urate, it also eventually overcomes the diminished alkalinity of the kidney, produced by the inflammatory trouble and prevents it hindering the excretion of urate that comes to it in the blood.

Treatment of the skin counteracts the effects of uricacidæmia on its circulation.

A milk and farinaceous diet aids the alkaline treatment by diminishing acidity, it reduces the amount of albumen that has to be acted upon by the hampered liver and skin, and it does as little as possible to add to the urate accumulation.

In chronic cases it appears to be good treatment to clear the blood of uric acid, by retaining it with acids, opium, iodides, or nitrites, which relax the arterioles, free the circulation through the kidney, increase the urinary water, and diminish the albumen (I mean an absolute, not a relative diminution, merely), while the diet is such as will not provide an excess of albumens to be metabolised by the damaged organs (liver and skin), or increase the formation or introduction of urate, above what is absolutely necessary for the continuance of life.

I also narrated above, a case in which nature did, by means of fever, what we attempt to do by acids, opium, and nitrites; the fever (of measles) raised the acidity, drove the urates out of the blood, relaxed the arterioles, and produced such a diuresis, that in a few days, a pretty extensive anasarca had been removed; the bearing of this on the causation of anasarca in Bright's disease hardly needs pointing out. If the urine in health is inversely as the urate in the blood, or the urate excreted along with it (see p. 93), then the anasarca of Bright's disease may be a mere exaggeration of what occurs in physiological conditions.

The diuresis which is known to follow an attack of paroxysmal hæmoglobinuria (*Lancet*, vol. ii., 1889, p. 1086) is another instance of the same thing; here, the rising temperature, doubtless with rising acidity, which often follows the attack, clears the blood of urates and frees the kidney circulation, so that all the water, which had accumulated in the blood and tissues during the uricacidæmia of the attack, runs off.

Before leaving these subjects, I must just mention a case narrated by Semmola,[1] because it illustrates several points I want to make as clear as possible. A woman, about the climacteric period, goes to see a medical man on account of feeling ill, and having a little skin eruption, he examines her water and finds sugar; he therefore puts her on a diabetic diet, but after some weeks she feels no better, and comes to Semmola, who finds that she has now no glycosuria, but an albuminuria in its place, and he thereupon makes the most instructive remark, that we are not dealing, either with diabetes, or with Bright's disease, but with a failure in combustion, *i.e.*, with a failure in the metabolic activity of the liver, skin, &c.; give such a patient excess of sugar, she would have glycosuria, or excess of albuminoids, albuminuria.

What I have suggested is, that uric acid, by interfering, as I have shown it does, with the circulation in the skin, brain, kidneys, liver, and other organs, as the muscles, may produce such a failure of function on their part, as will bring about incomplete combustion, and failure in metabolism; which, under some conditions, will result in hetero-albuminæmia and albuminuria. The secondary result of this being some kidney irritation, which may, according to Semmola, go on to the production of the structural changes met with in nephritis, though no doubt the uricacidæmia, by its effects on the circulation, directly contributes something to the structural alterations found in all the organs and tissues after death, including the kidneys.

It is obvious then, that in Bright's disease, we are dealing with a general, not a local disorder; and that to look upon nephritis as synonymous with Bright's disease, is to mistake a part for the whole.

The indications for treatment will obviously vary with the stage at which the trouble has arrived. Where the albumen excreted is all diffusible, and where it has only been passed occasionally or for a short time, there is every reason to believe that the kidneys are still sound and that diminution of animal food, or restriction of it for a time to milk only, will promptly stop the albuminuria. Then, if the diet is permanently altered so as to make severe uricacidæmia impossible in the future, no further trouble need be anticipated.

[1] *Archives de Physiologie*, 1883.

On the other hand, where serum albumen is passing, and has probably been passing for a considerable time, there is a lesion of the kidneys in addition to structural alterations in the skin, muscles, liver and other glands, and even if cure is possible, it will not follow at once on a mere change of diet.

Under these conditions the indications are : (1) To diminish the work of the metabolic tissues by giving animal food in its most assimilable form (milk). (2) To improve the circulation in these tissues by keeping the blood clear of uric acid. (3) To improve the circulation in, and prevent the atrophy of the skin, by such measures as warm clothing, climate, baths, massage and friction. And if we can do all this we may neglect the kidney entirely, for, once it is relieved of the cause of its trouble (the diffusible albumen and the altered circulation), it will slowly improve, and the excretion of serum albumen will diminish so far as the organic lesions are capable of improvement.

As regards our second indication, clearing the blood of uric acid, milk diet will go a long way towards attaining our object ; but in so far as there is already much uric acid stored in the body which on this diet will be dissolved out and pass through the blood, we must give some drug which will keep the urates out of the blood for a little till we can get the metabolic tissues into better condition, and probably the iodides with occasional doses of mercury are the best drugs for this purpose and may be continued for a long time. Semmola recommends the iodides, but does not explain their action, as I am now in a position to do. (See p. 62.) Their good effect here is precisely similar to that in headache, epilepsy, asthma, phthisis and skin diseases, and is due to their stopping uricacidæmia, lowering tension and improving the circulation. It may occasionally be well to give salicylates for a week or so to carry off any urate accumulations which the iodides may produce, but further experience is required with regard to this.

CHAPTER XIV.

Glycosuria and Diabetes Mellitus.

Glycosuria and diabetes mellitus have interested me for a considerable time because they appear to have some relation to uric acid, a relation which, as in the case of headache and mental depression, has been noted by several observers.

While thinking over this relation I was led to try the effects of salicylate of soda (without any knowledge that it had been previously used by others), and the results in many cases (see paper on "The use of Salicylate of Soda in Diabetes Mellitus and its Connection with Gout," *St. Barthol.'s Hospital Reports*, vol. xxv.) were so remarkable that this seemed to me to form another link in the chain connecting this disease or disorder of function with uric acid.

Sir A. Garrod says ("Gout and Rheumatic Gout," p. 472): "In the course of practice I have seen several cases in which gouty patients have become affected with saccharine diabetes, or glycosuria," and he narrates the case of a gentleman of 60 who had had gout for twelve years when diabetes suddenly came on, and for more than four years there were no gout attacks. Then the diabetes was checked and the gout soon returned.

Sir W. Roberts says (Urinary and Renal Diseases," ed. iv., p. 256): "The subjects of obesity and of the gouty diathesis are very prone to a mild form of diabetes."

Professor Latham (*British Medical Journal*, 1886, vol. i., p. 737) has written about a form of diabetes which originates, he believes, in some error in the metabolism of muscular tissue, and he says that in this form of the disease salicylic acid treat-

ment is of the greatest importance, and remarks that these patients often have excess of uric acid in their urine, and suffer from neuralgic pains in the joints and limbs.

Then the late Dr. James Anderson in an extremely interesting paper in the *Ophthalmic Review* (February-April, 1889), mentions in many places the connection of gout with diabetes, and at p. 18 says: "Many clinical facts go to show that gouty arthritis and diabetes mellitus are in certain cases merely transformed symptoms of the same diathesis, not present at the same time but one taking the place of the other." This, as will be seen, corresponds exactly with my previous quotation from Sir A. Garrod.

Dr. Anderson also makes several interesting quotations from Fagge's "Principles and Practice of Medicine," to the effect that both gout and diabetes are due to disorder of hepatic function.

Now it seems to me that some hyperæmia or congestion of the liver, is nearly the only fact in the morbid anatomy of diabetes, about which there is any considerable unanimity of opinion among pathologists. Thus, as mentioned by Sir W. Roberts (previous reference, p. 275-276) Dr. Wilkes believes that the liver of diabetes can be distinguished by its appearance (especially its firmness and dark colour) from that of other diseases. Dr. Dickinson sees signs of long-continued hyperæmia in the livers of diabetic patients, and Prout observed a gorged condition of veins terminating in the portal system in the same class of patients.

Dr. Saundby, in his lecture on the "Morbid Anatomy of Diabetes," says that the liver is generally enlarged, though he lays special stress on the wasting of the pancreas, and urges its further examination. (*Lancet*, 1890, vol. ii., p. 381.)

Dr. Pavy again (*British Medical Journal*, 1883, vol. i., p. 863-866) credits diabetes to a vaso-motor paralysis of the chylopoietic circulation which allows arterial blood to be supplied to the liver in place of venous.

It seems probable also that the various brain and peripheral lesions which sometimes cause glycosuria, act by affecting directly or indirectly the liver circulation, as Frerichs (*Uber den Diabetes*) points out that puncture of the fourth ventricle only causes glycosuria when the liver contains glycogen.

Now there is evidence to show that some amount of congestion of the liver is very commonly associated with gout, and

speaking of the symptoms of the most common form of gouty dyspepsia, Sir A. Garrod says (*loc. cit.*, p. 231-232): "These are generally accompanied with sluggish circulation in the portal system and congested livers;" and he further speaks of fulness and tenderness in the hepatic region as symptoms of this congestion.

The occasional association of glycosuria with ague is, perhaps, an instance of some influence on the circulation of the liver and spleen causing glycosuria.

We seem, then, to have arrived at this point, that there is a condition of liver congestion which is common in gouty dyspepsia, and bears no doubt some relation to uric acid and its presence or absence from the blood.

On the other hand, we have glycosuria in the pathogeny of which congestion of the liver is a very common feature, and this glycosuria has been noticed by several observers to bear a relation to the uric acid diathesis and to gout.

Now the relation of glycosuria to gout is, as we have seen, that the one alternates with and replaces the other; where there is glycosuria there is no gout and *vice versâ*. Now gout corresponds with the precipitation of urate in the joints and its comparative absence from the blood, so that with absence of urate from the blood there is no glycosuria.

But when a gouty patient goes for some time without an attack in his joints, he does so probably because something has increased the alkalinity of his blood so that it now takes up instead of depositing urate, and there is uricacidæmia and excessive excretion of urate in the urine; this is the opposite condition to that of gout and with this there may be (as we have seen) glycosuria.

So that glycosuria corresponds with excess of uric acid in the blood (uricacidæmia) the opposite condition to that of gout.

But congestion of the liver also corresponds to excess of uric acid in the blood; for Sir A. Garrod says (*loc. cit.*, p. 231-232): "The more prominent symptoms of the dyspepsia connected with the uric acid diathesis may be thus summed up: heartburn and eructations, oppression, and frequently sleepiness after food; a feeling of distention in the epigastrium at times accompanied with tenderness; some fulness over the hepatic region, the edge of the liver projecting a little below the ribs, and being occasionally

tender to the touch; the tongue much furred, red at the tip and edges, a disagreeable and clammy taste in the mouth, and the saliva and buccal secretion often more adhesive than natural." In two words, there is dyspepsia with its natural result, uric-acidæmia; this latter accounting for the oppression and sleepiness and the scanty saliva and clammy taste in the mouth; and in chapter xiii. I have given notes of a case in which marked enlargement of the liver accompanied a uric acid storm, and pointed out that I had myself had very similar experience of the effects of uricacidæmia on the liver.

Now Dr. W. M. Ord has pointed out (*British Medical Journal*, 1889, vol. ii., p. 965) that general high tension may cause an excess of blood in the liver and so glycosuria; and I have shown that arterial tension is directly as the uric acid that is circulating in the blood, therefore uricacidæmia will cause high tension, and this will produce congestion of the liver and glycosuria (p. 271).

The causation of glycosuria is thus theoretically complete, and it agrees with the experience of clinical observers that it alternates with gout and corresponds with the absence of gouty arthritis, that is, with the presence of uricacidæmia.

I may say also that my experience agrees absolutely with that of Sir A. Garrod, and that in my own case congestion of the liver always corresponds with uricacidæmia, and to such an extent is this the case that I have come to believe that I can produce some congestion of the liver at pleasure by affecting the uric acid.

It is interesting to remember in this connection that cirrhosis of the liver is sometimes attributed to sclerosis of arterial capillaries (*Gazette des Hopiteaux*, Aug. 4, 1888), and that Professor Semmola has long been in the habit of treating this trouble with milk diet and large doses of iodide of potasium, which would relax the capillaries. (See *Progrès Médical*, Dec., 1888, p. 533.)

But in Dr. Ord's paper above referred to, there are many points of very great interest, some of which I must mention at greater length, as I believe that the knowledge which we have now obtained of the action of uric acid on the arterioles, will enable us to explain a great many of them.

It had occurred to me some time ago to enquire, if glycosuria has this causation (*i.e.*, is due to congestion of the liver, which

again is due to the general high tension produced by uric acid), ought we not to meet with it in that disease in which high arterial tension is more marked than in any other, namely, chronic interstitial nephritis? From my own experience I was not able to answer the question, but on turning to Dr. Ord's paper, I was interested to find that he says (previous reference, p. 966): "We not infrequently find that people presenting in a typical form the symptoms of contracting granular kidney have also glycosuria." I have certainly seen several cases in which albuminuria and glycosuria appeared to alternate with each other, but whether these were cases of granular kidney I could not say; they appeared to me, however, to be almost certainly gouty cases.

Then Dr. Ord narrates, at considerable length, a case in which typical angina pectoris co-existed with glycosuria, and it would be impossible to find a case more to the point as regards the argument I am here bringing forward.

The patient, age 62, suffered at first along with his glycosuria, from low spirits and sleeplessness (very marked signs of uric-acidæmia). Then he had an attack of quinsy, in which, as is usual during fever, the sugar disappeared, but was replaced by albumen. (Note the uricacidæmia would also disappear in the fever.)

A little later he began to have angina, which afterwards during an attack of gastric catarrh became very severe.

Now there is hardly any condition which is more certain to produce intense uricacidæmia than gastric catarrh (see p. 85 and 189), and this would completely account for the increase of the angina, and with this increase of angina there was an increase of the amount of sugar in the urine.

I should be inclined to explain the sequence of events in this most interesting case as follows:—

First, slight uricacidæmia as evidenced by irritability, depression and loss of sleep; this producing general high tension which, through its effects on a weak heart, produced back pressure and congestion of all behind it, hence congestion of the liver and glycosuria.

Later on the congestion of the liver produced secondary congestion of the stomach and duodenum, and this, acting with some other slight cause, brought about gastric catarrh.

This last, again, produced nausea and vomiting which resulted

in a great fall of urea and acidity; and again, as the result of the fall of acidity, the uricacidæmia became intense; this more and more overtaxed and dilated the heart, the angina increased and became incessant, there was consequently increased congestion of the liver and increased glycosuria, and the patient finally died in an attack of angina.

Dr. Ord is inclined to invoke the nervous system as the cause of the high tension, though he says: "But in a preponderance of the cases presenting glycosuria together with symptoms of angina, the evidence of primary neurotic disturbance has not been so strong."

I have shown that uric acid will contract the arterioles and produce high tension, and we had here in action all the causes which will produce uricacidæmia, and all the signs of its presence, and I have no doubt that the urine also contained a great excess of uric acid, so that it appears to me to be quite unnecessary in any such case to invoke the unknown action of the nervous system. I do not deny that the nervous system can produce such an effect, but I assert that in the case in point, uric acid, and uric acid alone, did produce all the symptoms from the irritability, mental depression and loss of sleep to the congestion of the liver and glycosuria and the dilatation of the heart and fatal angina.

In an interesting paper on "Angina" ("International Clinics," Second Series, vol. vi.), Professor T. J. Mays points out that the effects of uric acid on the circulation afford a very complete explanation of several important points in its causation, as it is accompanied by a slow pulse, and is very often worse in the morning hours when there is most uric acid in the blood, and, further, like migraine and epilepsy, it may be preceded by feelings of exaltation and well-being. (See chapters vi. and vii., and the causation of fatigue and chloroform syncope, chapter viii.)

I have now shown that glycosuria has been observed to alternate with gout, and that this alternation probably means that it is contemporaneous with excess of uric acid in the blood (uricacidæmia).

I have shown that uricacidæmia contracts the arterioles and produces high arterial tension, and Dr. Ord has suggested that high arterial tension produces congestion of the liver and glycosuria.

My thesis also rests on the further facts of which I shall now

give details—(1) that acids (which, as I can show, clear the blood of uric acid and prevent uricacidæmia) are useful in glycosuria, and that certain mineral waters containing excess of sulphates which, like acids, also clear the blood of uric acid are equally useful in the cure of the disorder; and (2) that salicylates, as observed by myself and others, are very useful both in glycosuria and diabetes, and that they also clear the blood, liver, and other organs of uric acid.

The point about which there seems to be least room for doubt is that glycosuria alternates with gout, and is commonly contemporaneous with uricacidæmia; and supposing that the uricacidæmia is the cause of the glycosuria there are obviously other ways in which it may bring about this result besides that sketched out above in which it produces congestion of the liver. In this case there is excess of sugar in the blood and glycosuria because excess of sugar passes from the liver; but supposing that the liver is not thus affected, and that only the normal amount of sugar passes into the blood, it may still come to be in excess in the blood if it is not used up and destroyed in the general circulation; and it seems to me that uric acid, by producing contraction of all the arterioles, may, and probably does, interfere to an important extent with the metabolism of the muscles, skin, etc., and may thus bring about glycæmia and glycosuria through deficient destruction of sugar. At this point I think there is an interesting parallel in the pathology of "curare diabetes" in which the excess of sugar in the blood is supposed to be due to its not being used up in the paralysed muscles. (See *Archiv. für Anat. and Physiol.*, 1891, p. 476.)

Before leaving these theories I will mention one fact that seems to me of interest, namely, that, as observed by Sir W. Roberts ("Urinary and Renal Diseases," p. 255) women suffer less than men after forty-five; he attributes this relative immunity to the early decline of sexual activity; but I have shown that menstruation and especially dysmenorrhœa produce uricacidæmia, and a cessation of these disturbances may mean that the blood remains at this period in women moderately free from uric acid for some time, but I shall have to speak of the effects of menstruation again. (See case Mrs. C., further on.) With regard to the effects of acids, it is recorded, as I have mentioned before (*Practitioner*, 1891, vol. i., p. 193), that Sir W. Foster, in 1871, gave several

patients suffering from diabetes considerable doses of lactic acid, which improved the diabetes, but produced considerable pain and swelling in the joints; and this most valuable record proves several points of importance: first, that diabetes or glycosuria was present in these cases with excess of uric acid in the blood, or the acid would have had nothing to act upon; secondly, the acid acting, as I have shown that it does, in diminishing the alkalinity of the blood and reducing its power of holding uric acid in solution, caused it to be deposited or retained in the joints where its presence gave rise to an arthritis indistinguishable from that of acute rheumatism. (See chapter xvi.)

We have here, I think, a strong light thrown upon the causative connections of both rheumatism and diabetes: the condition (rising acidity) which cleared the blood of uric acid produced the one disease while relieving the other; just as mental depression, which is due to uricacidæmia, clears up when an attack of gout is produced.

I have also used acids with apparent benefit in some cases of glycosuria under my own care, and I was led to do so by reasoning that they would probably clear the blood of uric acid and have to some extent the same effect as salicylates, and without having any knowledge of Sir W. Foster's cases.

In my paper in *St. Bartholomew's Hospital Reports* (vol. xxv., p. 11, *et seq.*) I have pointed out what has been said about the great effects of certain waters as those of Contrexéville, Carlsbad, and Brides-les-Bains in curing diabetes, and have suggested that these waters owe their efficacy to the excess of sulphates they contain; as sulphates, especially sulphate of soda, act as I have shown, the part of acids, interfere with the solubility of uric acid, and clear the blood of it. (See *Medico-Chirurgical Trans.*, vol. lxxii.)

Before I go into the action of salicylates and give notes of my cases treated by them, I may perhaps mention shortly a few points about their effects on uric acid.

A salicylate then increases the solubility of uric acid, and must for a time increase the quantity contained in the blood: but though it does this the effects of uric acid in the blood seem to be modified (possibly by its being present as salicyluric acid and in a state of complete solution) and it neither affects the arterioles so greatly as uric acid combined with an alkali only, nor does it produce any headache.

But though we get salicyluric-acidæmia as the first effect of giving a salicylate this does not last very long; the uric acid is in a condition of perfect solution, it passes quickly through the kidney and out of the body, and, as I have pointed out, the great excretion of urate under salicylates occurs on the first two or three days of their action, and, after that excretion falls away almost to the level of formation: thus it comes about that after the first day or two of their action there is never any great amount of urate in the blood.

The effects of salicylates, therefore, resemble those of acids and sulphates in that they clear the blood of uric acid, and all these have this also in common—that they diminish or stop glycosuria or diabetes.

There are one or two other points of interest with regard to these substances which I may just mention. Acids are commonly used in conditions of slight congestion of the liver; sulphate of soda is supposed to have a special action on the liver, and salicylate of soda again is said to render the bile more fluid and watery; but acids, sulphates, and salicylates also, as we have seen (chapters ii. and iii.), increase the urinary water, and I have suggested that they produce this effect by freeing the arterioles of the kidney from the contraction produced by uric acid; is it not probable, I might say certain, that they produce precisely the same effect on the arterioles of the liver, and for that matter on those of the whole body? Hence, acids and sulphates relieve congestion of the liver by improving the circulation through it, and salicylates render the bile more fluid by the same action, just as they make the urine more copious.

But the salicylates have this great advantage, that they clear the blood of uric acid by removing it from the body while the acids and sulphates clear the blood (as do also opium, mercury, the iodides, iron, lead, and lithia, &c.) by retaining it in the liver, spleen, joints, and other tissues.

Prominent among other drugs that have been found useful in diabetes are opium and antipyrin, and I have shown (pp. 32 and 37) that they raise the acidity of the urine, and probably as regards uric acid act the part of acids and clear it out of the blood; therefore all drugs that are useful in diabetes have this effect in common, that they clear the blood of uric acid, and clinical experience and observation go to prove that glycosuria is asso-

ciated with an excess of uric acid in the blood, and may in some of the ways I have suggested be actually due to such excess; its well-known relationship to gout and the uric acid diathesis being thus susceptible of a simple explanation. And there are two pathological conditions, which having the same action as the drugs just mentioned, in clearing the blood of uric acid, also for a time put an end to glycosuria or diabetes. One of these conditions is a fever, and the other is the effect produced on metabolism by a surgical operation. The fact that these conditions do diminish the sugar in diabetes was mentioned at a meeting of the Royal Medical and Chirurgical Society, in October, 1892 (see *Lancet* and *British Medical Journal*, Oct. 29), but no explanation was attempted.

After what I have already said as to the action of fevers, in diminishing the excretion of uric acid in the urine, and clearing it out of the blood, and consequently relaxing the arterioles, causing diuresis and a soft pulse, and a general increase of metabolism, both in the liver and other tissues, and of the post febrile rebound which follows their departure with excessive excretion of uric acid, slow high tension pulse, scanty urine and subnormal temperature, and diminished metabolism, in all of which points their effects exactly resemble those of opium, mercury, the iodides and other drugs; I need not do more than point out that, like these drugs, fevers supervening upon a glycosuria or diabetes, diminish or stop the excretion of sugar, and the fact is as well known as the explanation is simple.

There is one point, however, that I would specially like to bring to the notice of those who may make clinical observations on the effects of fevers on the excretion of uric acid, namely, that the blood and urine are most completely cleared of uric acid during the first few days of the fever, and it is then that the pains resulting from their precipitation on joints and other fibrous structures are most likely to be met with. (In my own person I have several times correctly diagnosed a slight rise of temperature from pricking and shooting pains in my joints with a diuresis. See also note on p. 277.)

But there may be a considerable amount of uric acid, both in the urine and in the blood as the temperature comes down, even while it is still a degree or two above normal; for the solubility of uric acid in the blood depends on its alkalinity, and for any

given alkalinity the quantity in solution will be greater, the more urate there is available for solution.

Now the rapid metabolism at the onset of a fever quickly diminishes the alkalinity of the blood, for I have shown that, as regards the urine, urea and acidity practically always rise and fall together, because they are two results of the same metabolism.

But, as time goes on, and the patient becomes worn out with the fever and deficient income of food, metabolism will run down in spite of the temperature being still raised; the alkalinity of the blood will again increase, and it will take up much uric acid, partly because of its altered reaction, and partly because the stores of uric acid in the body have been increased by the first action of the fever: for this reason there is a marked lessening of the dicrotism of the pulse in fevers some little time before the temperature touches normal.

But if these facts are not kept in mind, if the uric acid is estimated with sole regard to the fever but no regard to the metabolism, the diminished excretion at the beginning of the fever may be partly balanced by plus excretion near its end, and most contradictory results will no doubt be obtained. My results show for instance, that early in pneumonia there is almost no uric acid in the blood, and yet after death there is more in it than after almost any other disease. We can now see that the fluctuation in one direction is the result of the previous fluctuation in the other.

A fever therefore diminishes the sugar in the urine of diabetes, because by clearing the blood of uric acid and relaxing the arterioles, it quickens the metabolism throughout the body, and up goes urea as a result of this, just as we have seen that it goes up when the blood is cleared of uric acid by any other means, hence the glycosuria diminishes or disappears, especially during the rising temperature of the onset of the fever, because the combustion of sugar is complete. Similarly when excess of uric acid in the blood diminishes the metabolism throughout the body, urea, as we have seen, (pp. 85 and 263) goes down.

Now the effect of a surgical operation on the metabolism is practically the same as that of a fever. I was much struck with this some years ago, when I chanced to obtain for another investigation the urine of a woman, for one or two days before and after the operation of abdominal section. The rise of urea

after the operation was enormous, reaching twice or even three times its previous height, and I explained this to myself by supposing that there was very active metabolism at the seat of operation, and that the patient was thus placed on a highly nitrogenous diet at the expense of her own tissues.

I have unfortunately mislaid the notes of this case, and cannot now give the exact figures: but Dr. Young, resident medical officer of the Royal Hospital for Children and Women, kindly investigated some cases for me, and I am indebted to him for the following notes:—

E. K., age 47	...	June 6 ...	264 grs. urea
,,	...	,, 7 ...	124 ,,
(Plastic operation for ventral hernia.)			
,,	...	June 8 ...	422 ,,
,,	...	,, 9 ...	528 ,,
,,	...	,, 10 ...	401 ,,
,,	...	,, 11 ...	322 ,,

Sarah H., age 49. Ovarian Tumour.

Before operation	...	...	151 grs. urea.
1st day after ,,	...	...	192 ,,
2nd ,, ,, ,,	...	...	354 ,,
3rd ,, ,, ,,	...	...	188 ,,

M. H., age 56. Ilio-femoral abscess.

Before operation	...	...	232 grs. urea.
1st day after ,,	...	...	276 ,,
2nd ,, ,, ,,	...	...	452 ,,
3rd ,, ,, ,,	...	...	345 ,,

In each of these cases the urea doubled after the operation, the greatest excretion of urea taking place on the second day after it; and for some cases in which the effects of an operation were still more marked. (See *Lancet*, vol. i., 1893, p. 1413.)

Then, as I have shown, the acidity of the urine rises with the urea, and urates in the blood and urine vary inversely as the acidity, hence a surgical operation, which causes a marked rise in urea, will clear the urates out of the blood, relax the arterioles and increase the metabolism.

I will now also give a figure to show the remarkable way in which, in a case of glycosuria, the uric acid and sugar fluctuate together.

The curves are from the case of Rebecca M., age 45, who was

under my care at the Metropolitan Hospital in 1889, suffering from enlargement of the spleen, excess of white cells in the blood, and glycosuria.

I have also pointed out (p. 45), that in cases where the spleen is enlarged, there is nearly always a great excess of uric acid in the urine, and others have pointed out, just as I should expect, that it is in excess in the blood in these cases.

It follows, therefore, that this is just the condition of things in which we should expect to find just what we do find in this case—a glycosuria as the result of the uricacidæmia, which is common in such cases.

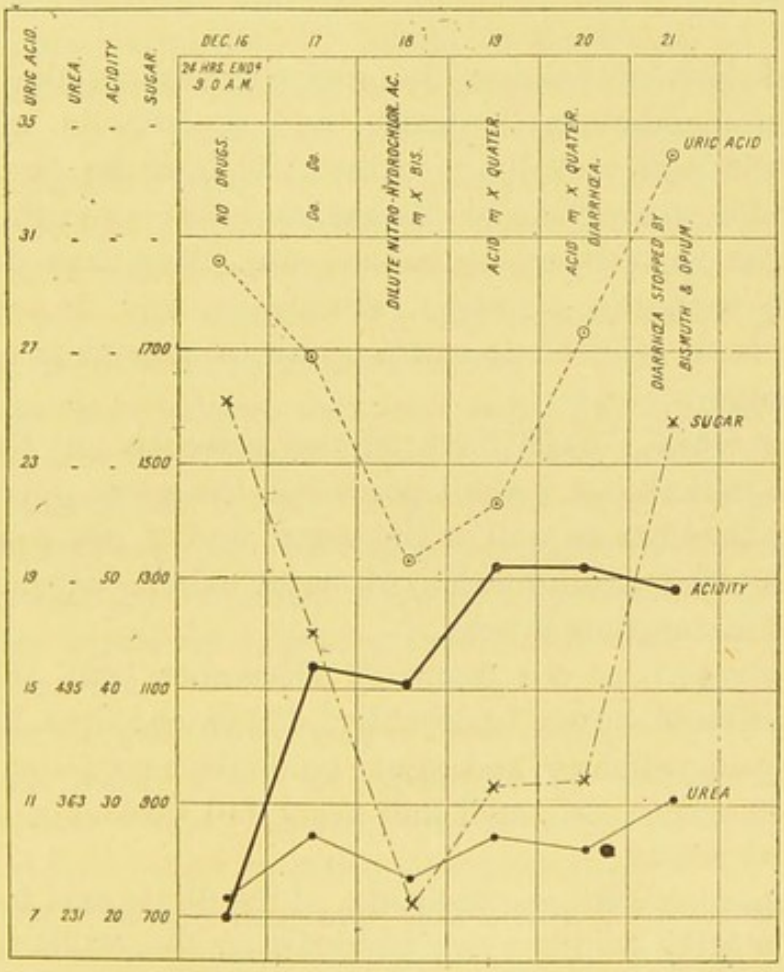

FIG. 34.—CURVES OF EXCRETION OF URIC ACID AND SUGAR IN A CASE OF GLYCOSURIA.

On December 16 (fig. 34), we see that uric acid and sugar are both high, urea and acidity low; on the 17th urea rises a little and acidity still more, and with this there is a fall of uric acid and a fall of sugar. There must have been some cause depressing the acidity on the 16th, for it rises on the 17th out of proportion to the rise of urea.

Talking of low acidity reminds me of the fact of which we shall see instances among my cases, that patients suffering from diabetes or glycosuria, often say that alkalies, such as the bicarbonate of sodium or potassium, do them harm; and we see in this figure the way in which they do it, namely, by increasing the uricacidæmia, and in this figure the uric acid is high, because the acidity is low, and the sugar is high because the uric acid is high. So that not only do all drugs, fevers, and surgical operations, which diminish uricacidæmia, do good, but drugs like alkalies, which increase uricacidæmia, do harm.

Some of my readers will probably remark that alkalies are often of great use in diabetes, and may reduce the sugar very markedly.

Now I have mentioned in previous chapters the effects of alkalies on metabolism in health, and the way in which they increase uric acid and diminish urea; is it to be doubted that they have the same effect in disease, and that when they reduce the sugar, as there is no doubt they may, they have done it by interfering with the digestion, absorption, and metabolism of food, and have reduced the urea quite as much, or even more than the sugar.

And in what I shall have to say presently on the use of salicylates in diabetes, I shall point out the great importance of estimating the urea as well as the sugar, and of not regarding as a curative effect a diminution of sugar which depends on an equivalent dimunition of urea.

But to return to our figure on December 18th, the patient took ℥x. of acid. nitro. hydrochlor. dil. twice: urea fell a little and acidity also slightly, and would no doubt have fallen more but for the acid taken; uric acid and sugar fall decidedly and reach their lowest points.

On December 19th she took ℥x. of the dilute acid four times; urea rose a little, acidity more decidedly as the result of the acid taken; uric acid and sugar both rose a little, though uric acid bears much the same relation to urea that it did on the previous day.

On the 20th the patient again took ℥x. of the acid four times a day; but now she has some diarrhœa, so urea falls a little. Acidity did not rise; uric acid rose, but sugar remained about the same as on the 19th.

This is the only occasion on which uric acid and sugar did not move in the same direction, and I think this is due to there being, on account of the diarrhœa, a lessened absorption of food, and therefore a lessened income of sugar. (Compare previous remarks on the effects of alkalies.)

On the 21st the diarrhœa was stopped by means of bismuth and opium mixture, and urea rose; but acidity fell as the result of leaving off the acid and the effect of the diarrhœa on the previous day. Probably the acidity was really low in the early part of this day (21st), and this allowed of the large urate excretion which we see; later in the day, as the result of the opium, it rose sharply, and the balance of the two fluctuations resulted in only a slight fall of acidity in the whole 24 hours. I constantly meet with such results in my own experimental work on excretion. And lastly, on this day there is a great rise of sugar corresponding fairly well with the rise of uric acid.

Taking the whole figure, I think it must be acknowledged that the curves of uric acid and sugar run parallel to each other in a remarkable way, and some of my other cases to be given presently seem to show much the same thing.

I here therefore suggest that just as we saw in the previous chapter that albuminuria and Bright's disease may originate in a lowering of metabolism which brings about hetero-albuminæmia, albuminuria and nephritis, so also is glycosuria or diabetes due to a similar lowering of metabolism which hinders the final combustion of carbohydrates and, leaving them to circulate in the blood, produces glycæmia.

The lowered metabolism may in each case be due to uric acid, which brings about a deficient capillary circulation in all the great metabolic tissues: its evil effects being no doubt either increased or diminished by concomitant conditions.

It follows from this reasoning that clearing the blood of uric acid will do good, while increasing the amount it holds in solution will do harm; and I have just pointed out that acids, opium and other drugs which clear the blood of uric acid are useful, while fevers and surgical operations which have the same effect on uric acid, are well known to diminish the output of sugar; while on the other hand alkalies, which increase the uric acid, do harm.

Acids and opium often have a similar good effect in albuminuria; and a fever may not only, as I have shown, diminish the dropsy, but also reduce the total output of albumen.

I shall now go on to show that salicylates which clear the blood of uric acid by effecting its elimination are also very useful in glycosuria and diabetes.

Mary A. D., age 55.—An out-patient at the Royal Hospital in January, 1888. Complains of thirst and irritation of vulva. Urine pale amber, 1020; 3.2 per cent. sugar. Alkalies and nux vomica no effect. After four weeks of salicylate urine 1014. No sugar. Drinks much less. Salicylate left off and in two weeks, urine 1020 and 3 per cent. of sugar, and again salicylate reduced it to 1011 and no sugar.

Mrs. C. age 45.—May, 1888. Urine 1032-1040 and containing 5 per cent. sugar. Put on salicylate, and in seven days' time the urine was 1035 and 2.5 per cent. sugar. Treatment continued, and two weeks later urine dark amber, 1030, and only .5 per cent. of sugar. Drinks much less.

I then altered her diet; left off the excess of meat she was taking, and put her on milk, fruit, and vegetables, and so long as she took the salicylate these did not increase the sugar, except on one occasion when it reached 1.6 per cent. She found that potatoes were worse than other vegetables, and produced diuresis (probably from the large amount of alkali they contain interfering with the action of the salicylate). (See p. 21.) She attended for many months; the sugar in spite of diet keeping about one per cent.

Her husband then left the district in search of work, but a year later, October 1889, she came back asking for more of the medicine which had done her so much good. She is paler, and has wasted considerably since last seen in 1888. Urine is now 1030 : contains 5.7 per cent. of sugar, urea 1.5 per cent., and uric acid .08736 per cent., uric acid to urea 1—17, urea to sugar 1—3.8. A large excretion of uric acid, and no doubt uric-acidæmia contemporaneous with glycosuria. Fourteen days later, after a course of salicylate, the urine only contained .6 per cent. of sugar.

November, 1890.—Returned again after considerable absence, and again salicylates reduced her sugar in a week to 2.5 per cent. She was, however, upset by home troubles, and could not take her medicine or attend regularly.

February 16, 1891.—Took her into Royal Hospital, Waterloo Road. No drugs except a little dilute phosphoric acid, a little

sal volatile for feelings of "weakness and sinking" (patient probably indulges in alcohol at home for these feelings). Urine of twenty-four hours 990 cc. 1046. Sugar 7.1 per cent., urea 1.6 per cent., uric acid .06720 per cent. Uric acid to urea 1—23. Urea to sugar 1—4.4. Total sugar 2.4 oz.

On February 26, after ten days on salicylates, urine was 1335 cc. 1034, urea 1.5 per cent., sugar 3.6 per cent. Urea to sugar 1—2.4. Total sugar 1.6 oz. Salicylates had here reduced the total sugar, and had also reduced it relatively to the urea, which is perhaps the safest guide of all.

She remained in for several weeks, during which the sugar was reduced to 2 per cent. and less with the relation of urea to sugar 1 to 1.2. Patient, however, became unruly, dissatisfied and disobedient, possibly owing to alcohol and stimulants being cut off, and took her discharge.

During the first part of her time in hospital she was menstruating, and this appeared to increase the feelings of sinking and faintness, as it doubtless also lowered the acidity, produced increase of uricacidæmia, and also interfered with the full action of the salicylates.

Henry F., age 54, November, 1888.—"Glycosuria and acute gout," under the care of Sir Dyce Duckworth, who very kindly allowed me to examine the urine.

Urine on two days without treatment gave 2000 and 1650 cc. Uric acid to urea 1—48 and 1—33. Urea to sugar 1—6.2 and 1—5.9.

There was here a minus excretion of uric acid with glycosuria, but no doubt when the uric acid has produced the condition which gives rise to glycosuria, this may go on for a day or two when there is no uricacidæmia; besides the fact that the relation on the twenty-four hours was 1—48 and 1—33, is no proof that there was not some uricacidæmia for several hours during the alkaline tide of each day.

After three days on salicylate the total sugar was less by 200 grs. than at first, and the relation of urea to sugar was 1—4.8.

But the patient was now up and free from his gout, so the examination could not be carried further. The notes of his case do not say whether he had the glycosuria along with the acute gout or not. He continued to take salicylate for some time, as he

said it did him good; but he also indulged freely in beer and brandy, and this latter would no doubt aid the uric acid in producing congestion of the liver.

Jane B., age 33, Nov., 1888.—Complains of weakness and languor; drinks all day long and passes much water, especially during last two months. She first noticed excessive thirst about eighteen months ago, the time of commencement of her last pregnancy. Urine pale amb., 1043, urea .6 per cent., uric acid .02016 per cent., sugar 10 per cent. Uric acid to urea 1—30. Urea to sugar 1—17. She was given some instructions about diet and put on alkalies and nux vomica. These did no good, and at the end of a week sugar was still 10 per cent. She was put on salicylate, Dec. 1, and told to try and estimate amount of water in twenty-four hours.

Dec. 8.—Urine 1040; sugar 9 per cent.

Dec. 15.—Passed 20 pints of urine yesterday; thinks she has passed considerably more than this. Urine 1042. Sugar 8 per cent. Urea to sugar 1—12.

After this sugar fell steadily to 7 per cent., with relation to urea 1—8.7, and she began to gain weight and get more colour.

In April, 1889, during my absence salicylate was stopped and nux vomica and alkalies repeated; the mixture made her worse, and she threw it away after two or three doses. (It is a remarkable fact that nearly all these patients with glycosuria or diabetes say that alkalies make them worse and acids make them feel better. The former increases, but the latter diminishes uric-acidæmia.)

She did not come again till Aug. 17, when she was obviously worse—pale, feeble, and with quick pulse. No urine brought; given salicylate again.

Aug. 24, 1889.—Better, and less thirst: when thirst is great nothing under two pints of water is any use. Urine to-day 1040, sugar 10 per cent.

In September urine had fallen to ten pints a day, sugar 6 per cent., and urea to sugar 1—6; and at the end of this month sugar was 5.5 per cent., and urea to sugar 1—5.5.

In October, sugar 5 per cent., and urea to sugar 1—5, and she got on so well that she refused to leave her children and come into hospital.

The urine was reduced to less than one-half of the original

amount, and the percentage of sugar to one-half also, so that the total sugar was reduced to one-fourth of the original quantity, and the relation of urea to sugar altered from 1—17 to 1—5.

She improved and felt better in every way while taking the salicylate, and while the sugar was diminishing she steadily increased in weight.

She continued to attend for many months after this, and so long as she took the salicylate did well. I found that small doses of morphine increased its effect and gave her for some time gr. $\frac{1}{6}$ in pill three times a day. By this means sugar was reduced to 4.5 per cent., and on one occasion to 3.5 per cent. But unfortunately, in the spring of 1890, there was a change: she again became pregnant, and this produced a considerable amount of vomiting; this interfered with the taking and action of the salicylate, and she went rapidly down hill. She still obstinately refused to come in, and soon ceased to attend. My last note is dated Oct. 7, 1890, when she was much weaker and worse and salicylate had been left off for some time and bismuth and other treatment of symptoms made use of. As she refused to come in, in spite of all I could say, nothing more could be done, and I fear that she soon died.

The case, however, illustrates well the power of salicylates in what no one probably will deny was severe diabetes; and I have no doubt that the drug prolonged her life by at least two years, as when I first saw her I did not expect her to live a month, and but for her unfortunately again becoming pregnant (which is in itself strong testimony to the improvement in her condition), still better results might have been obtained.

Another case is that of Winifred H. F., age 8 years, who was admitted under my care at the Royal Hospital for Children and Women, January 22, 1891.

Complained of thirst and nocturnal urination; pale, wasted; weight 2st. 5lbs. Some increase of liver dulness, and constipation.

Urine 2220 cc. pale amber, 1040. Sugar 5.5 per cent., uric acid to urea 1—33. (No excess of uric acid [?] due to phosphoric acid given as a drink.) Urea to sugar 1—5.5, urea per lb. 10.3 grs. She was put on diet; no drugs except a little dil. phosphoric acid. The sugar fell to 5 per cent. and then to 4.1 per cent., but urea fell very considerably also, and on February 9 it

was only 4.6 grs. to lb. Diet here was interfering seriously with nutrition, and though sugar fell, urea fell more; very different from what had occurred in the previous case with salicylate.

She was given some salicylate, but it unfortunately upset the stomach and made the failure of nutrition greater; sugar and urea both falling considerably. Her pulse on several occasions was relatively slow, showed considerable high tension and occasional intermissions.

It was therefore stopped, and she was given two pints of milk and some brandy. She had previously been taking food (diabetic diet) badly: but she liked the milk and began to improve on it, and urea and sugar both increased.

February 12.—When urea got back to 9 or 10 grs. per lb. and sugar to 5 per cent. salicylate was again given in small, slowly increasing doses. Both urea and sugar, however, continued to increase, though on February 18 urea was to sugar 1—3.2, and on the 19th 1—3, and on the 21st 1 to 2.9, and on 24th 1 to 2.3.

Salicylates now apparently caused some dyspepsia and diarrhœa and all drugs were therefore stopped, and on February 28 urea was to sugar 1—3.3. It looked, therefore, as if the salicylate had had some effect in lessening the sugar relatively to the urea.

March 2.—Slight rise of temperature, and sugar fell in consequence, the urea relation being 1—2.2.

Salicylate was begun again gr. vii. four times a day, but again diarrhœa followed its use and some tr. opii was given.

March 4.—Urea to sugar 1—3.1 ; salicylate had not begun to act.

March 5.—1—3.

March 7.—1—2.3.

March 12.—Opium stopped. Given codeina gr. $\frac{1}{4}$ three times a day, and salicylate gr. x. four times a day, urea to sugar 1—2.2.

March 18.—Rather more languid. Codeina stopped and liq. morph. hydroch. ɱx. given four times a day with the salicylate.

March 26.—Going on much the same, but there is occasionally some vomiting, and the dirrhœa has not completely ceased. Urea to sugar 1—2.2. Total urea 739 grs. or 22 grs. per lb. She is now taking a considerable quantity of milk and is not kept on strict diabetic diet, as it was found that she took this badly, urea diminished, and she got into a lethargic condition, which disappeared as the diet was improved.

March 27.—Some diarrhœa again, so salicylate and morphine stopped.

March 31.—No diarrhœa or vomiting; given codeina gr. $\frac{1}{4}$ three times a day.

April 4.—On codeina; temperature raised to 101°. Takes badly and has some nausea: urea to sugar 1—2.5 (effect of fever), but urea has fallen to 540 grs., 16 grs. per pound.

April 6.—Not so well; very drowsy, especially in the morning after breakfast, when she falls asleep and does not wake for several hours. Takes badly, some nausea. All drugs stopped, milk increased to three pints, brandy 2 ozs.

April 9.—Better and brighter much; takes better, but urine has increased in quantity and specific gravity. Salicylate and morphine mixture repeated.

She died on April 19 (while I was away for a holiday) with some symptoms of diphtheria, and another child in the ward had a suspicious throat and was isolated.

Permission for a *post-mortem* examination could not be obtained, so the exact nature of the case remains in doubt. There was no optic neuritis, and such vomiting as occurred seemed to be the result of drugs rather than of any central cause. The only physical sign was a moderately well-marked increase of liver dulness.

As to drugs, the salicylates on several occasions reduced the sugar relatively to the urea, and that without in any way reducing the urea.

The codeina diminished urea and sugar, but did not diminish the sugar relatively so much as the salicylate. On one occasion it appeared to cause drowsiness.

Diabetic diet was an absolute failure, causing a great fall of urea and producing a lethargic condition which would no doubt have been fatal if the diet had not been improved; possibly diet was begun too suddenly. In such cases it is obviously of the greatest importance to examine the urea; anything that interferes with the taking and digestion of food will reduce both sugar and urea, but this is not a curative action. Salicylate reduced the sugar relatively to the urea, and the child fully held her own while taking it. Unfortunately, however, it appeared to produce some nausea and diarrhœa.

I shall also give the notes of a case in which salicylates given

along with small doses of calomel eventually acted well, though at first they appeared to fail.

W. H., aged 36. Admitted under my care in the Metropolitan Hospital, January 18, 1893. Complains of increase of appetite one month, and increase of thirst two weeks.

His father is alive and well, but suffers from lumbago and piles occasionally.

His mother has "rheumatics" in the hands. He has five sisters, who are well.

Patient has not had any fevers, not even the influenza.

His tongue is slightly red at the tip and edges, but not specially clean.

His bowels are constipated.

There are no physical signs.

January 19.—Weight, 99 lbs. 10 ozs. Put on a modified diet, gluten bread, Milk Oii., and imperial drink without sugar. No potatoes, bread or sugar.

January 22.—Urine, 74 ozs.; sp. gr. 1035. Acid. No albumen. Sugar, 3.1 °/₀ = 1059 grs.: urea, 2.4 °/₀ = 819 grs.; relation, 1 to 1.2.

January 24.—Bowels opened by mist. sennæ co. Thirst is rather less.

January 28.—Sodii salicyl. gr. xv. Out of aq. menth. pip., given every six hours. Weight, 103 lbs.

February 1.—Urine, 58 ozs.; sp. gr., 1036; sugar, 3.1 °/₀ = 830 grs.; urea, 2.6 °/₀ 6 grs.; relation, 1 to 1.1.

The salicylate appears to cause some nausea, and he is not taking his food so well. Try to take the salicylate in powder.

February 4.—Urine, 56 ozs.; sugar, 1.4 °/₀ = 361 grs.; urea, 2.4 °/₀ = 620 grs.; relation, 1 to 0.58. Weight, 103 lbs. 8 ozs.

Appetite still bad, so salicylate stopped and iodide of sodium, gr. vii., given in place of it three times a day.

Here we see again that the sugar has fallen greatly down to almost one-third of the amount on January 22, but urea has also fallen by as much as 200 grains, and we know that this was due to deficient income of food from nausea and loss of appetite, and if we add, say, 200 grs. to the sugar on this account, the relation would come out nearly 1 to 1, or close to what it was on February 1.

February 8.—Urine, 98 ozs.; urea, 2.1 °/₀ = 950 grs.; sugar,

2.0 °/₀ = 905 grs.; relation, 1 to 0.95. Iodide increased to gr. x.

February 10.—Urine, 80 ozs.; urea, 2.4 °/₀ = 837 grs.; sugar, 3.1 % = 1,145 grs; relation, 1 to 1.2. Weight, 103 lbs. 8 ozs.

February 14.—Iodide left off, and salicylate again given in different form.

February 15.—Urine, 90 ozs.; urea, 2.4 °/₀ = 997 grs.; sugar, 3.3 °/₀ = 1,372 grs.; relation, 1 to 1.3.

February 18.—Urine, 94 ozs.; sp. gr., 1037; urea, 2.7 °/₀ = 1,130 grs.; sugar, 2.6 °/₀ = 1,088 grs.; relation 1 to .96. Weight, 105 lbs. 6 ozs.

February 22.—Urine, 86 ozs.; sp. gr., 1031; urea, 2.3 °/₀ = 913 grs.; sugar, 2.5 °/₀ = 993 grs.; relation, 1 to 1 (nearly).

February 25.—Urine, 102 ozs.; sp. gr., 1036; urea, 2.3 °/₀ = 1,082 grs.; sugar, 2.9 °/₀ = 1,365 grs.; relation, 1 to 1.2. Weight, 106 lbs.

Here again, though the salicylate at first reduced the sugar relatively to urea, the improvement was not maintained.

Liq. morph. hydrochlor. ♏ xii. was added to each dose of the mixture.

March 1.—Urine, 46 ozs.; urea, 2.7 °/₀ = 572 grs.; sugar, 1.2 °/₀ = 254 grs.; relation 1 to .44. Weight, 106 lbs. 4 ozs.

Here again, a great diminution of sugar, but also a great fall of urea, and no doubt the salicylate and the morphine upset appetite and digestion and accounted for this.

March 8.—Urine, 71 ozs.; sp. gr., 1032; urea, 2.0 °/₀ = 710 grs.; sugar 2 °/₀ = 710 grs.; relation, 1 to 1.

March 10.—Urine, 78 ozs.; sp. gr., 1024; urea, 2.2 °/₀ = 791 grs.; sugar, .8 °/₀ = 287 grs.; relation, 1 to .36. Weight, 106 lbs. 8 ozs.

Here is some improvement, and, as urea is rising, it is probably due to the drugs.

March 14.—Urine, 64 ozs.; sp. gr., 1025; urea, 2.7 °/₀ = 797 grs.; sugar, .5 °/₀ = 147 grs.; relation, 1 to .19. Allowed a small bit of toasted bread twice a day.

March 17.—Urine, 70 ozs.; sp. gr., 1023; urea, 2.4 °/₀ = 776 grs.; sugar, .75 °/₀ = 241 grs.; relation, 1 to .3. Weight, 107 lbs. 4 ozs.

March 24.—Weight, 108 lbs. 8 ozs.

March 29.—Urine, 74 ozs.; sp. gr., 1036; urea, 2.4 °/₀ = 751 grs.; sugar, 3.3 °/₀ = 1127 grs; relation, 1 to 1.5.

Toast was left off and liquor pancreaticus given, also calomel gr. ½ twice daily.

April 1.—Urine, 62 ozs.; urea, 2.7 °/₀ = 773 grs.; sugar, 2.5 °/₀ = 716 grs.; relation, 1 to .9; weight, 106 lbs.

April 11.—Has had vomiting in the morning since 6th. Urine, 44 ozs.; urea, 3.5 °/₀ = 711 grs.; sugar, .5 °/₀ 101 grs.; relation, 1 to .14.

April 14.—Weight, 108 lbs.

April 19.—Urine, 54 ozs., sp. gr., 1026; urea, 3.3 °/₀ = 822 grs.; sugar, .7 °/₀ = 174 grs.; relation, 1 to .21.

April 22.—Has had some pain in connection with the sac of a femoral hernia; but this has now been relieved by rest and ice locally. Urine, 52 ozs.; sp. gr., 1021; urea, 2.1 % = 508 grs.; sugar, .15 = 20 grs.; relation 1 to .03.

April 26.—Urine, 44 ozs., high colour; sp. gr., 1030; urea, 3.8 °/₀ = 671 grs.; sugar, .4 °/₀ = 81 grs.; relation, 1 to .1; weight, 104 lbs. 12 ozs.; given claret, ozs. ii.

April 29.—Urine, 64 ozs.; sp. gr., 1019; urea, 2 °/₀ = 591 grs.; sugar, .1 °/₀ = grs.; relation, 1 to .09.

May 3.—Urine, 38 ozs.; sp. gr., 1030; urea, 3.4 °/₀ = 595 grs.; sugar, .03 °/₀ = ? *nil.*

Here sugar is reduced to *nil*, though urea is as high as at last note. Toast allowed again.

Is still on salicylate, morphine, calomel, and liq. pancreaticus.

May 6.—Urine, 48 ozs.; sp. gr., 1029; urea, 3.2 °/₀ 708 grs.; sugar none; weight 104 lbs.; liq. pancreaticus left off.

May 10.—Quantity and sp. gr. as at last note; still no sugar.

May 13.—Weight 106 lbs.

May 19.—As sugar continued to be absent and he was going on well he was allowed to go out, taking the salicylate mixture and calomel with him.

August.—Attends at the hospital every few weeks and continues the mixture and the calomel powders. Sugar remains absent, and he is quite holding his own.

I think the credit of this improvement remains with the salicylate and calomel; the liq. pancreaticus appeared to have no effect whatever; the salicylate and morphine also appeared to account for an improvement in March.

As mentioned in a previous case morphine helps the action of a salicylate, and I believe that it may do this by keeping up the

acidity, and preventing any of the uric acid, which salicylates bring through the blood, from getting into combination with an alkali, because it is the combination of uric acid with alkali, which affects the vessels and does all the harm.

And my object in giving calomel was just the same, namely to keep the blood clear of uric acid combined with alkali; and calomel does this by directly combining with the uric acid (see p. 35.), and it appears from the results in this case, that it helps the action of the salicylate more than the morphine does, possibly because its effect is independent of acidity; and under certain conditions the morphine may not be able to raise the acidity. (See p. 31.)

Considering that in this case, there was only 3.1 % of sugar to begin with (though by the way, this was on diet), I should have expected a more decisive result with salicylates alone: but their partial failure was, I think, largely due to their being taken badly, and producing nausea: when they do this they are no use in any case. They are also no use when there is nausea or vomiting from other causes (See Case of Jane B.). I believe because there is then so much alkali in the blood, that a good deal of the uric acid is sure to combine with it.

Still, I consider that given along with acids or small doses of morphine or calomel, the salicylates are the most useful drugs we possess for the treatment of these troubles, and they act by eliminating uric acid, and so clearing the blood of it. I have often seen the sugar greatly reduced by opium or codeine, but they have also appeared to me to reduce urea very considerably, at the same time, while with the best action of salicylates urea rises.

Frerichs says that salicylates reduce sugar by interfering with digestion; but in several of my cases salicylates not only greatly reduced the sugar without reducing urea, but the patients steadily gained weight while taking them.

In my paper on the use of salicylates in diabetes I mentioned that two cases had been reported as cured by them, and since my paper, I have heard from others who have followed up my suggestion and used them with great benefit (see Dr. Mansel Sympson, *Practitioner*, August, 1891), and Dr. Brooks, of Lincoln, read a paper before the Lincoln Medical Society in 1891, on the use of salicylates in diabetes.

In suggesting that glycosuria and diabetes may be due to a failure of combustion and a slackening of metabolism, which, again, may result from the vascular effects of uric acid, pointed out in previous chapters, I am very far from claiming that all such cases are due to uric acid.

I believe, however, that the connection between gout and diabetes is both wider and deeper than has hitherto been suspected; and that some of the riddles of this sphinx (Frerichs, "über den diabetes," p. 275), may be solved by admitting provisionally the power of uric acid over metabolism; and by thus admitting it provisionally, we are by no means bound to forego any opportunity that may offer of putting the point to the most careful tests we can devise.

The indications for the treatment of such a glycosuria or diabetes are to diminish the introduction and formation of uric acid, and to clear out that which has accumulated in the body. A long course of salicylates will satisfy the last indication; and if they, at the same time, remove the sugar, we ought, I think, to go gradually back to ordinary diet, and even beyond it; eventually reducing animal food to small quantities of milk, cheese, and egg; and, unless we are able to do this, I believe that relapse is often merely a question of time.

CHAPTER XV.

Gout.

Since I first discovered that in driving uric acid out of the blood while curing an attack of headache or mental depression, I produced pricking and shooting pains in the joints, the explanation of the arthritis of gout has never seemed to me to be a very difficult matter.

And it still seems to me that when we have obtained a complete knowledge of the chemistry and solubility of uric acid under the conditions present in the human body, we shall have no difficulty in explaining completely all the phenomena of gout.

I am quite prepared to undertake to produce a uric acid arthritis in anyone provided my instructions are carried out, but the clinical result will often resemble what is described as the arthritis of rheumatism rather than that of gout.

From my point of view the arthritis in both diseases is due to uric acid, which, in acute rheumatism, is suddenly driven into a large number of joints, where, however, it remains generally only for a short time, and is then completely removed, but in gout a great part of the uric acid in the blood is (generally by the action of some external causes) concentrated on one particular joint, where it is not only present in greater quantity, but remains longer than in the case of acute rheumatism.

I believe, however, that it is quite possible by imitating nature to produce at pleasure an arthritis which would, by a third person, be called rheumatism or one which would be pronounced gout.

If, in the arthritis called rheumatism, the uric acid is removed in the course of a few days, only microscopic lesions are produced, which are quickly repaired, and leave no trace after death, but if injury, cold or other external causes prevent the removal of the urates from one or more of the joints they may set up and maintain an irritation in its fibrous structures which may obtain a considerable hold on the tissues and go on smouldering by itself after the uric acid has been removed. In this way are brought about extensive lesions of structure which even after acute rheumatism are sometimes visible after death, and where uric acid has been again and again precipitated (from causes I shall presently speak of) on the irritated areas, changes commonly called rheumatoid are at length produced.

These rheumatoid changes, when extensive, should be regarded as in part the direct effects of the irritant uric acid, and in part due to the smouldering on of the irritation it causes, so that I have been accustomed to speak of the uric acid as the fire, and the rheumatoid changes as the ruins, and obviously the treatment of the ruins is a very different matter from that of the fire. To remove the uric acid is the best treatment of the fire, but that will not rebuild the ruins.

I was interested to see that in his address in the section for diseases of children at Bournemouth, Dr. Goodhart speaks very strongly as to the relationship of gout and rheumatism. Thus (*British Medical Journal*, vol. ii., 1891, p. 252) he is reported as saying: "In the first place I hold that gout in children is not to be discriminated from acute rheumatism," and further on he says: "I think that in summing up what gout is we must say that under some circumstances or at one period of its life gout is acute rheumatism."

I have shown that under all circumstances and at all periods gout is rheumatism and rheumatism gout, and that while both are due to uric acid the clinical picture varies with age and other factors, the action of which can be completely explained, but I am glad to see so great an authority as Dr. Goodhart arriving at the same conclusion from different premisses.

It is necessary to make these preliminary remarks, or the position I shall take in this and the following chapter would not be understood.

What evidence have we that uric acid produces such irritation as that I am speaking of in the fibrous structures?

I have often quoted Sir A. Garrod's remarks on the effects of wines, &c., and have suggested that it was the acid in these beverages that drove the urate into the joint and produced the inflammation, of which the pricking pain is the sign; he says (p. 245): "Where a few glasses of wine, ale or porter quickly and invariably produce in any individual an inflammatory affection of a joint, such inflammation is of a truly gouty character," and in the lines preceding this he mentions how some sufferers have heat, throbbing, stiffness, and pain in their gouty joint after two glasses of port or a single glass of champagne. Now it is easy to demonstrate that champagne is intensely acid, more so than the other wines and malt liquors mentioned, and Dr. Brunton (in the debate on my paper on "Salicylates and Rheumatism," *Proceedings of the Royal Medical and Chirurgical Society*, April, 1890, p. 109) mentioned a case in which champagne had apparently produced symptoms of poisoning by its great acidity.

There can then, I think, be no doubt that these beverages acted as doses more or less strong of acid, and drove the uric acid out of the blood into the already irritated joint.

Then, as mentioned by Sir W. Roberts in the above debate, Ebstein has shown that urate dissolved in phosphate of soda produces irritation and morbid change when injected into the cornea, while the phosphate alone produces none.

Then again, Sir A. Garrod has pointed out (previous reference, p. 292) that the cartilages and fibrous tissues of joints have but little vascularity, and are less alkaline than other tissues, or than the blood, and if this is so we can easily see why urates should become "less soluble and more easily retained" (to quote Sir A. Garrod's words) in the neighbourhood of joints.

Further, the joints in the old are probably both less vascular and less alkaline than those of the young, so that such external causes as injury or cold will more easily diminish their alkalinity in the old, and produce a local concentration of urate and a gouty arthritis.

In the young, on the other hand, the effects of local cold or injury will be less, the alkalinity will be better maintained, and it will only be when general causes act all over the body, such as severe chill and wetting during perspiration, that the alkalinity of all the joints will be reduced at once, and the more general

arthritis of acute rheumatism will result. Hence the joint irritation produced by urates tends to be general and acute in the young (acute rheumatism), local and subacute or chronic in the old (gout).

With regard to the action of acids I have produced pricking and shooting pains in my own joints—many scores of times, when using them to remove the uric acid headache or mental depression, and in a case of gout under the care of Sir Dyce Duckworth in St. Bartholomew's Hospital, where he kindly allowed me to examine the urine, I was able to show (*St. Barth. Hosp. Reports*, vol. xxiv., p. 217) that every time the acidity rose the uric acid fell below the urea (relation 1—45 or 1—50, a great retention of uric acid), the temperature tended upwards and the pains increased and became severe, and conversely whenever the uric acid was above urea (relation 1—24, excretion in excess of formation)—whether this result was produced by salicylates or alkalies—the pains diminished or ceased, and the temperature subsided. I hope that anyone who is still sceptical about the effects of acids in gout will look at the curves given in the above paper, and will then try acids on themselves or on any gouty patient who will consent to the experiment, and I am confident that the results will remove all doubts, and for a similar observation in an attack of gout, see clinical note by Dr. Liddell, *Lancet*, vol. ii., 1893, p. 631.

In reference to physiological relations I would point out that the attack of gout commonly occurs at night during the acid tide, when the excretion of uric acid is at its lowest, and during the course of the attack the pains are always worst and the temperature highest at night. The curves in my paper above referred to show this well. Sir A. Garrod (previous reference, p. 42) quotes from Sydenham's description of the attack in which the hour of onset is mentioned as 2 a.m., and on p. 44, still quoting from the same authority, we find this statement: "One thing, however, is constant—the pain increases at night and abates in the morning." I hope that no one who has followed my reasoning will have any difficulty in understanding the reason of this. It is in absolute accord with my statement, that the excretion of uric acid is inversely as the acidity, and that when uric acid fails to be excreted it is retained in the joints and irritates them.

As regards season Sydenham's account is equally emphatic.

He says (p. 42): "Towards the end of January or the beginning of February suddenly and with scarcely any premonitory feelings the disease breaks out."

That is to say, at the very coldest season of the whole year, when, as I have shown, the acidity is highest and the excretion of uric acid least. (See p. 15.)

But indeed, the whole of Sydenham's description can be easily explained in terms of uric acid excretion by anyone who is conversant with it. Thus he says (same reference, p. 42: "But a few days before this (that is the attack) torpor comes on and a feeling of flatus along the legs and thighs." This means a slight fall in acidity (no doubt due to the stomach derangement he speaks of as a forerunner of the attack) and a plus excretion of uric acid, and its excess in the blood causing "torpor," or as I have described it, mental depression. Then see what happens; he goes on: "Besides this there is a spasmodic affection, whilst the day before the fit the appetite is unnaturally hearty. The victim goes to bed in good health and sleeps," and at 2 a.m. is roused by the pain.

We have seen that there was dyspepsia with fall of acidity and uricacidæmia with "torpor" as its sign. Then the stomach improves: "the appetite is unnaturally hearty." Up go urea and acidity at a time when the blood is highly charged with uric acid, and the natural result is that it is driven into the joints, and this occurs just at an hour when the acidity has been rising for some time and is nearly at its highest point. (See p. 90.)

We can now see all our factors quite clearly, almost as well as if we had produced the attack ourselves. (1) Dyspepsia producing a fall of acidity and uricacidæmia. (2) Improvement of digestion and appetite raising acidity and driving the uric acid out of the blood into the joints. Can anything be more simple? and this sequence can be imitated at pleasure to any required extent.

Why does gout come in January and February? (1) Because during part of November, the whole of December, and most of January the weather is cold. This diminishes the excretion of acids in perspiration, and keeps the acidity of the urine high (Sir A. Garrod) and the alkalinity of the blood low, hence, during this period, the excretion of uric acid falls short of its formation and introduction, and it is retained and accumulated in the

body. (2) When, at the end of January, dyspepsia lowers the acidity for a day or two, there is a large store of uric acid in the body which is at once washed out into the blood, producing intense uricacidæmia with "torpor" as its sign. (3) On this supervenes a sharp rise of acidity which quickly clears the blood of uric acid, driving it into the joints. (4) During the "good health" of the day before the attack the patient has probably taken a little extra exercise as well as a little extra food, and during the exercise he has produced a little warmth and diminished alkalinity in some of the joints of his feet. This has not subsided when the rising acidity of night not only prevents its fall, but increases it. Hence, at 2 a.m., certain joints in the feet are the least alkaline structures in the body, and the whole, or nearly the whole, of the uric acid in the blood is concentrated upon them, and acute pain and inflammation result.

The whole thing is a fluctuation in the excretion of uric acid, which, as I have said, can be imitated to any required extent.

In experimental work a gout attack can be produced by acids or any drugs which directly or indirectly raise the acidity or otherwise interfere with the solubility of uric acid.

From what has been said, it must be obvious that an acid may fail to produce an attack of gout for several reasons. (1) It may fail to be absorbed from gastric irritability (nausea, vomiting, &c.), or it may irritate the stomach, and prevent its own absorption and that of food also, and so lower rather than raise acidity. It is specially likely to do this when given too concentrated, or in too large a quantity at one time. (2) When absorbed it may be overpowered by alkali present or produced from other sources (as debility, perspiration, &c.). It is always necessary, therefore, to see that an acid given raises the acidity of the urine. (3) There may be no uric acid in the blood owing to its previous removal by a course of salicylates or other solvents, and then there is obviously nothing for the acid to act on, and no gout results.

Other things which interfere with the solubility of uric acid (such as iron, lead, mercury, lithia, zinc, manganese, calcium, &c.) may also produce an attack of gout, but compared to acids they are rarely met with in nature, and are not generally so powerful in action, as a good supply of alkaline phosphates or

other alkali easily prevents their producing much retention. Still at night, when the acidity is high, they will produce a little or increase any pain that is present.

Of iron salts, Sir A. Garrod says (p. 383): "These preparations, when indiscriminately given to gouty subjects, are apt to excite paroxsyms of their disorder, and are, for the most part, contra-indicated."

That lead precipitates gout attacks is so well known that I need hardly quote anything concerning it, but Sir A. Garrod has shown that gout is much more common among those exposed to lead, such as plumbers and painters. He also pointed out that uric acid is almost invariably present in the blood in cases of lead poisoning.

I would remark, in passing, that it is during the secondary action of lead that there is uricacidæmia. Its primary action is, as I have shown, to diminish the solubility of uric acid to bring excretion below formation, and to retain it in the body, and at this time there is little or none in the blood. Then, when from dyspepsia or intestinal pain (due to urate of lead in the intestinal walls, see pp. 28 and 192), the urea and acidity fall, the retained uric acid is washed out into the blood stream, and uricacidæmia with slow high tension pulse accompany and follow the lead colic. If my researches are correct, the slow high tension pulse which is often very marked in plumbism may be taken as proof positive of the presence of excess of uric acid in the blood, and the pulse can be quickened and its tension reduced by drugs that act on uric acid, and they may produce gout. Again, I have in my own case often produced (as it is easy to do) both the primary and secondary action of lead.

As to mercury, I have shown that its administration brings the excretion of uric acid below the level of formation (*British Medical Journal*, vol. i., 1890, p. 1241, and fig. 11, p. 36), and clears the blood of it, producing mental well-being, relaxed arterioles, and quick low tension pulse and diuresis, all results of relaxed arterioles.

It also resembles lead in that it produces in my own person at least some intestinal pain of a griping character.

Sir A. Garrod says of it (p. 236): "It is a well-established fact that metallic impregnation is capable of inducing pains in the extremities, which bear a close resemblance to those of

rheumatism." Artificers exposed to mercurial vapours often suffer from what is termed "neuralgia mercurialis."

With regard to lithia, I must refer to what I have said of its action on p. 29. My results show that it diminishes the excretion of uric acid, and at the same time relaxes the arterioles and quickens the pulse, causes mental well-being and a free flow of urine, and when it does all this it generally causes, like lead and mercury, some pricking and shooting pain in the joints also.

Thus all things that increase the solubility of uric acid increase its excretion, clean it out of the joints, and do good in gout. Conversely all things that interfere with its solubility diminish its excretion, cause its deposit in the joints, and do harm in gout. (See case quoted on p. 159.)

In pathology we see that a gout attack is brought on by indulgence in wines and beers, which are more or less strongly acid. Champagne is about the most acid of wines, and the cheaper beers are generally more acid than those of better quality. I found acidity equivalent to 18 grs. of oxalic acid in a pint of 4d. ale, and 25 grs. in a pint of stout. Sherry 37 grs. in a pint. Port about the same. Claret 46 grs. to the pint, and champagne 49 grs. to the pint.

Sir A. Garrod says (p. 226): "As regards acidity, Dr. Bence Jones has ascertained that wines may be arranged in the following order, beginning with the least acid:—Sherry, Port, Champagne, Claret, Madeira, Burgundy, Rhine wines, and Moselle. All the wines are found to be more acid than malt liquors," but as the quantity of malt liquor taken is generally much greater than that of wine, the total amount of acid taken in may be greater in those who drink beer than in those who take wine.

Sir A. Garrod says (p. 212): "That women are less subject to gout than men is beyond doubt." He attributes this to difference in character and habits, and adds "besides which a most powerful counteracting influence exists in the presence of the catamenia during a considerable portion of their lives."

As to habits, women are generally less exposed to weather (cold and wet), and take less of beers and wines than men, and as to the catamenia I have shown that menstruation lowers acidity and produces uricacidæmia and a plus excretion of uric acid, and this occurring for four or five days in every month

may sensibly diminish the amount of uric acid that is stored in the body. (See p. 154, on mental depression and its relation to menstruation.)

As to the effect of age I mentioned some points at the beginning of the chapter, and shall speak of it again in the chapter on rheumatism.

I have also spoken of beers and wines, and cider no doubt acts in the same way as an acid. In estimating the effects of any of these beverages on different races, it is necessary to bear in mind the amount of meat or nitrogenous food they consume, as this determines the introduction as well as the formation of uric acid and obviously an acid will produce most effect and most quickly store sufficient uric acid to cause gout where it has most to work upon, and the formation and introduction are greatest. Thus in England beers produce more gout than in Germany, because the English consume more meat per head of population than any other nation in Europe. (See *Lancet*, vol. ii., 1890, pp. 409, 468 and 589.)

Speaking of nationality reminds me of the fact that the Scotch suffer from gout comparatively little, so that our brethren north of the Tweed have difficulty in finding cases on which to work. I have no doubt that this is due to the fact that the national beverage of the Scotch, namely, whiskey, contains little or no acid, and affects acidity but little, and the Scotch also, as a rule, eat less animal food than the English. If a Scotchman comes to England and drinks beer and wine and eats meat, he suffers from gout like the Englishman. Sir A. Garrod says: "The least acid of all alcoholic fluids are geneva and whisky."

(For similar facts about the incidence of gout in Persia see chapter xvii.)

It is generally agreed that excess of animal food is a cause of gout, and Sir A. Garrod quotes several authors to this effect, and he also says, on p. 230, "Cullen remarked that gout seldom attacked persons employed in constant bodily labour, or those who live much upon vegetable diet."

My own experience well illustrates this point. On ordinary diet my urea formation was from 500-600 grs. a day, and my uric acid 15 to 18 grs. On my present milk and vegetable diet urea is about 360 grs. and uric acid about 10-11 grs. per day.

With the high urea went high acidity, the solubility of the uric acid was often interfered with, excretion often fell below

formation and introduction, and much of it was retained in the body, and then, whenever acidity fell from any cause, there was intense uricacidæmia.

Now, with lower urea there is lower acidity. Nearly all the uric acid formed is excreted at once, and little or none is accumulated in the body. There are no stores to produce uricacidæmia, and hence I have now complete immunity from the uric acid headache.

The effect of exercise in producing a plus excretion of uric acid and so keeping off gout, as observed by Cullen, I have already gone into in speaking of the pathology of fatigue. (Chapter viii. and fig. 28.)

Dyspepsia may have an important influence, as I mentioned in speaking of Sir A. Garrod's quotations from Sydenham. It seems probable also, as pointed out by Bouchard, that acids may be formed under certain conditions or out of certain articles of food, and these would, no doubt, affect the solubility and excretion of uric acid, so long as they continued to be formed.

It has been assumed by several writers, notably by Murchison, that in certain conditions of functional disturbance of the liver there is an excessive formation of uric acid. If they mean that uric acid is formed in greater proportion to urea than 1 to 35, I can see no good evidence of it, and I look upon the excess of urates in the blood and urine as the sign of excessive excretion, the result of previous minus excretion or retention. If they mean that in certain liver troubles, especially those accompanied by slight fever, there is excessive formation of both uric acid and urea, in their normal relation I should raise no objection.

Among the symptoms of the dyspepsia connected with the uric acid diathesis mentioned by Sir A. Garrod (previous reference, p. 232) are many which I have attributed to uricacidæmia as "oppression and frequently sleepiness after food." "Saliva and buccal secretion often more adhesive than natural." I have pointed out that saliva is scanty in the uricacidæmia of the opium rebound, and at the time of the uric acid headache, mental depression, &c., in all cases no doubt due to the same cause, namely, contraction of arterioles by uric acid. "Accompanying these symptoms there is a scanty secretion of urine which is highly coloured and strongly acid." I have pointed out that the urine is scanty in the uricacidæmia of the uric acid headache and

mental depression, and that the water in fact varies inversely as the uric acid excreted along with it, and the water is scanty probably for the same reason that the saliva is scanty because the vessels of the kidney are contracted.

As to high acidity, that is only relative to the water. If the urine of 24 hours is saved it will be found that the total acidity is really considerably lower than that of the previous day, when there was less uric acid and more water.

Much sedentary work tends to produce gout. Sir A. Garrod quotes (p. 233) Sydenham as saying, "Whenever I returned to my studies, gout returned to me," and I have already given his quotation from Cullen about the preventive power of bodily labour.

I have pointed out that the excretion of uric acid is greater in summer than in winter, and Sydenham speaks of gout as a winter disease. Now, there is no doubt that a labouring man has, so to speak, summer all the year round. His exertions keep his skin constantly active. He gets rid of a large amount of acid in this way, hence the acidity of his urine rules low, and the alkalinity of his blood is well maintained; he therefore excretes uric acid freely, and retains but little in his body, and so, as observed by Cullen (previous quotation), he but rarely suffers from gout, and this is so almost without regard to his diet, for he excretes all the uric acid he introduces, as well as all that he forms. As to the acidity of the sweat, see also Heuss, *Monatsch. fur Prakt. Dermatol.*, band xiv., Nos. 9, 10, and 12, and *Lancet*, vol. ii., 1892, p. 1118. A sedentary man has not only higher acidity and retention of uric acid, but his circulation especially in peripheral parts like the hands and feet, is less well maintained, and as a result the alkalinity of the fibrous tissues in such parts is also less well maintained.

Though, as I have said, I used to have headaches when my life was not sedentary, I have no doubt that I could indulge in meat and beer with comparative impunity if I lived the life of a labourer.

After what I have said about the effects of summer, it is not surprising to find Sir A. Garrod saying (p. 235), "Gout is undoubtedly much less prevalent in hot than in temperate climates," though, no doubt, as he remarks further on, food and habits have also something to do with its absence.

The reverse effects of cold need hardly be gone into, but Sir A. Garrod says (p. 247) : "When cold acts as an exciting cause the effect is due, at least in part, to its arresting the secretion of the skin and checking the escape of acid from the surface," and my experimental experience is in complete accord with this statement.

Local injury will, no doubt, diminish the alkalinity of the affected part, just as fever diminishes the alkalinity of the whole body, and Sir A. Garrod says, "Local injury not only acts in exciting gout, but frequently determines the situation in which the inflammation will show itself. Thus, injury to the knee or ankle will usually cause these joints to be primarily affected, although the great toe, or some other part, may subsequently become implicated."

We shall see presently that in rheumatism local injury has the same effect, and compare the above quotation with what I have said as to the effects of exercise in determining the seat of the gouty arthritis.

Hæmorrhage is recorded by Sir A. Garrod as an exciting cause, and he attributes its effect to the "nervous depression" it produces. It seems to me, however, that another explanation is possible. First of all the blood is alkaline, and loss of blood is practically equivalent to removal of alkali from the body. Then it is well known that when the temperature is normal severe loss of blood from any cause will raise it, and fever, as we have seen, raises the acidity. We have, therefore, two results of severe hæmorrhage which, acting together, diminish the alkalinity of the blood and tissue fluids. This interferes with the solubility of uric acid, and tends to precipitate it upon certain of the least alkaline tissues, namely, the fibrous tissues in the joints and elsewhere.

That, as Sir A. Garrod relates, sudden stoppage of menstruation should produce gout, is not very extraordinary, for menstruation, as I have shown, is commonly accompanied by uricacidæmia and its signs, and any exposure to cold or febrile disturbance supervening upon this would, undoubtedly, drive the urate out of the blood into the joints, and it seems to me that in many of these cases the action of the nervous system, like that of Jupiter in ancient mythology, has been unnecessarily invoked from ignorance of the real cause.

Where the gout attack comes suddenly in the night and is in every way typical, there is not much to be said about the diagnosis, and salicylate of soda in sufficient quantity will very quickly relieve it, as in my case in *St. Bartholomew's Hospital Reports*, previously mentioned. It is necessary, however, to give sufficient, and if gr. xx. can be given every two hours for acute rheumatism, I fail to see why it should not, if necessary, also be given for acute gout; certainly neither disease can be expected to yield to a dose of gr. x. three times a day.

Where, however, the attack is not typical, where it is not markedly worse at night, where it is prolonged and chronic rather than acute and sudden in onset, and where it is much worse after exercise, no matter what is the time of day, while true gout is worse at night even though the patient has never moved out of bed all day, we may have to do with traumatic or surgical inflammation, and not with true gout at all. Here salicylates may have no effect whatever, and the proper treatment is by rest and fomentations as employed by the surgeon.

Such inflammation may occur in a joint which has been previously affected by true gout and may be the result of exercise, pressure, or strain acting on a joint damaged by urates.

This trouble in an old gouty joint is only too easily mistaken for true gout, and when salicylates fail to relieve, the reputation of the drug suffers when the diagnosis is really at fault. Colchicum may then be employed, and with the aid of rest the patient is cured.

Now colchicum has this advantage over salicylates, that it does good in both the conditions which are here possibly being confused: it relieves true gout by increasing the alkalinity of the blood and so facilitating the solubility and excretion of uric acid, and it also relieves a surgical inflammation by causing general depression of nutrition, absorption and metabolism, acting in this respect like antimony, aconite or free purgation.

I have never myself seen a case of true gout in which salicylates failed to cure, and I suspect that their alleged failure is often due either to insufficient dose or insufficient diagnosis of the condition present.

CHAPTER XVI.

Rheumatism and Morbus Cordis.

Much of what I have said about gout will apply also to rheumatism, and though they can often be clinically distinguished, I do not draw any hard and fast line between them, believing that the arthritis is in both cases due to the irritant action of uric acid on the fibrous structures of the joints.

I have suggested that salicylates cure acute rheumatism by effecting the elimination of urates, and I have further shown that as regards the action of salicin, salol and a salicylate, the latter has most power, dose for dose, in eliminating uric acid, and has also most effect over the arthritis, while salicin has much less effect on uric acid, and requires to be given in much larger doses, and salol is in both respects intermediate between the two. (See *Medico Chirurgical Transactions*, vol. lxxiii., p. 297.)

I have further suggested that the action of uric acid as an irritant of fibrous tissues may quite as easily account for the endocarditis and pericarditis of acute rheumatism, as for its arthritis. (See *Practitioner* of February, March and April, 1891.)

I have also remarked on several occasions, that while the chemistry and physics of uric acid appear to me to be capable of completely accounting for all the phenomena of acute rheumatism, and the action of all drugs and diet that are useful in treatment; as much cannot be said for any other theory of its causation.

For instance, no satisfactory explanation of the value of alkalies among drugs, or of milk and farinaceous diet, or again of hot baths, blankets, and other sudorifics in general management, can be given on the theory that acute rheumatism is due to a

miasm or microbe; while on the other hand, a comparatively rudimentary knowledge of the solubility of uric acid and the processes which promote its excretion and elimination will suffice to explain them all.

In reference to these points I have formulated the statement: "All substances which promote the free excretion and elimination of uric acid do good in the arthritis which is due to it, and conversely all substances which hinder its excretion and elimination do harm." (*British Medical Journal*, vol. ii., 1888, p. 10.) And the pathological condition which most hinders the solubility and excretion of urates (namely, fever) has just the same effects as the drugs which do this, and frequently precipitates an attack of general uratic arthritis; hence we are told by a writer in the *Lancet*, vol. i., 1893, p. 918, that "Enteric fever at its very commencement may present the picture of acute rheumatism." I believe that any acute fever may present this same picture, provided there was in the blood at the time the temperature began to rise, sufficient uric acid to irritate the joints when it is concentrated upon them; for fever diminishes the alkalinity of the blood, and diminishes its powers of holding urates in solution; and I have already pointed out in chapter xv. that the blood is in this way most completely cleared of urates at the beginning of the fever, which corresponds exactly with the observation of the writer, quoted above.

I shall now pass on to examine the points of difference between rheumatism and gout, and see how far the different conditions under which the uric acid acts at different periods of life will enable us to explain them.

My friend, Dr. A. E. Garrod, who mentions my researches on uric acid in the most kindly manner ("A Treatise on Rheumatism," p. 27,) yet objects strongly to my suggestion that acute rheumatism may be due to uric acid. He says: "Many objections present themselves to such a theory of acute rheumatism which appears to me to attach undue importance to the articular troubles, whilst offering no explanation of the occurrence of the cardiac and other visceral lesions of rheumatism." I believe, as I have already said (*Practitioner*, February, 1891, *et seq.*), that uric acid is quite capable of producing all these lesions, and I shall go into the matter presently; and Dr. Garrod goes on: "Again we have the fact that uric acid has not been found in the

blood of rheumatic patients, which Dr. Haig explains by supposing that this substance is driven out of the blood into the joints by the high and rising acidity due to the fever; but no deposit of sodium urate is found in the joints. Lastly, it is difficult to believe that the same *materies morbi* is capable of giving rise to two such different disorders as rheumatism and gout."

This last statement is somewhat indefinite, but I hope to be able to show that the differences are those of degree rather than of kind, and that they are due to differences in metabolic activity, in functional activity, or in chemical condition, which affect differently the solubility of uric acid, while the total quantity present also differs in the two conditions.

It has never been a matter of surprise to me that Sir A. Garrod was unable to find uric acid in the blood in acute rheumatism: on the contrary, if he had a found a large quantity in the blood it would have been a death-blow to my theory of the causation of acute rheumatism.

He does find it in the blood in gout because as I have previously said, gout is a local disease; in which the acidity of one or two joints is specially raised, and in these all the uric acid that the blood brings in their direction is rendered insoluble and retained, giving rise to irritation and inflammation; but there is no general clearing of the blood from uric acid except in so far as the specially affected joints take it up.

In acute rheumatism, on the other hand, the conditions are different; there is a general rise of acidity which clears all the uric acid out of the blood, driving it into the joints and elsewhere; little or none remains in the blood because the alkalinity of the whole circulating fluid is diminished; while in gout, though alkalinity generally is diminished, it is only in the specially affected joints that the urate is rendered completely insoluble.

This explains a fact previously mentioned, that when I intentionally produce an arthritis by giving acids, the clinical picture resembles rheumatism rather than gout, because I diminish the alkalinity generally, and drive the uric acid out of the blood into joints and fibrous tissues generally: if I want to imitate gout I must diminish the alkalinity generally, to some extent: but I must also produce local irritation and rise of acidity in a joint by a blow, seton, or other injury, and this will precipitate the uric acid locally, while the blood still contains some.

In further objection to my explanation Dr. A. E. Garrod goes on to say, "but no deposit of sodium urate is found in the joints." He evidently considers the fact that the urate is not found there after death, as equivalent to proof that it has never been there.

My researches have led me to take a very different view, and to believe that even in gout, where urate is deposited, so to speak, in mass, it may be removed so completely as to leave little or no trace of its presence after death, except the erosions in cartilage, &c., which some weeks, months, or years before death were completely filled up by it.

Much more so in acute rheumatism, where the urates are never present in mass, are only present for a few hours, and produce only a little interstitial irritation. So soon as the acidity which drove them into the joints falls away, and the alkalinity of the blood rises, the urates in the joints are quickly taken up in solution in the blood, and passing through it arrive at the kidney, and are excreted. Hence the excretion of uric acid is, as I have pointed out, directly as the alkalinity of the blood, and inversely as the acidity of the urine, a relation which holds both in disease and in heaith, and can be demonstrated artificially at any time by using drugs which affect the alkalinity (except lithia, see p. 29.) As previously pointed out Sir A. Garrod suggested that uric acid, when in the blood, is attracted differently by different organs, and that in certain organs, which for various causes are less alkaline than the blood, "the uric acid becomes less soluble and more easily retained." ("Lumleian Lectures," *British Medical Journal*, 1883, vol. i., p. 549.)

If this suggestion be granted, and if it be further granted, as also shown by Sir A. Garrod, that the cartilages and fibrous tissues of joints are both less vascular and less alkaline than the other tissues or the blood (see previous chapter), then the arthritis produced by uric acid is a simple matter of solubility, and can be produced at pleasure to almost any extent, and this, I have good reason to believe, is the case.

But there are other fibrous tissues in the body besides those of the joints, and what is to prevent them from being occasionally less alkaline and from suffering in consequence from a precipitation of uric acid upon them, and the irritation it sets up?

What about the fibrous tissues in the great lumbar fascia (lum-

bago) of those that form the sheaths of great nerve trunks (sciatica), and of those again that support the various coats of the intestinal walls (colic), of which I have already spoken, or of the fibrous tissues in the pelvic organs, and fascia especially in women not a few of whose pains and inflammations in these organs may have an identical pathology with that of gout of the intestines (chapter x.), and that some of these inflammations in women are rheumatic has, I believe, already been suggested by Dr. Gervis.

But there are fibrous tissues in a more vital organ than any of these, an organ which is sometimes said to be in part analogous to a joint, and is often affected along with the joints in acute rheumatism. I mean the heart.

Will anyone who has looked at a transverse section of the heart wall tell me that the visceral layer of the pericardium is not continuous with fibrous tissue, which fibrous tissue forms the fascia of the heart muscle and the fibrous tissue continuous with the endo-cardium on the opposite side of the wall the same?

Muscles become acid as the result of contraction (Foster, "Physiology," 1877, p. 49), and if in some regions of the cardiac muscle, in proximity to its fibrous investment, the products of functional activity and contraction are not quickly removed; the muscle and its adjacent fascia may have their alkalinity so far reduced as to form foci, in which the uric acid circulating in the blood becomes according to our premisses "less soluble and more easily retained."

Such retention, also in accord with our premisses, giving rise to local irritation, which still further reduces the local alkalinity, more uric acid is deposited, and so on till a considerable area of inflammation going on to proliferation of fibrous tissue and scar formation is the result.

If this may be the effect in the lumbar fascia, why not also in the pericardium and endocardium? The same causes that drive uric acid into the joints and set up arthritis may drive it into the fibrous tissues of the heart and produce endo- and pericarditis.

But as regards the endocardium at least, this is by no means the whole story, as there are causes just such as those which are active in the case of the joints, namely, friction and percussion, which may affect its alkalinity also.

Just as in the case of the joints, the heat and friction of exercise often determine which joints shall be least alkaline, and so

get the largest share of the uric acid ; so in the heart the fibrous tissues of the valves may suffer from friction and percussion, and so be rendered the least alkaline of all the fibrous tissues of the heart at a time when there is a general fall of alkalinity.

Now, the effects of exercise on the reaction of the valves of the heart will be greatest where the work and strain are most severe, thus possibly accounting for the incidence of the chief rheumatic changes in the left side during extra-uterine and the right side during fœtal life.

In this way any unwonted exertion or strain on the heart by giving rise to a little local irritation on the opposing surfaces of the mitral or aortic valves may diminish the local alkalinity, cause a local precipitation of uric acid and consequent irritation, and this irritation may, we will suppose, be repeated and repeated till what were at first scarcely visible pin point nodules of irritated connective tissue come at last to form well marked nodules and scars.

Such a process of reasoning helps us to understand how, what is at first a small local irritation in the mitral valve is carried on and on by a frequently recurring uric acid irritation, till the whole valve is reduced to the condition of a thickened scar, and we have to deal with the final stages of mitral constriction.

And if, as I believe, an excess of uric acid in the blood contracts all the peripheral arterioles and raises arterial tension (p. 88), it is clear that it must throw increased work on the left side of the heart, first of all on the aortic valves and then during systole, owing to the increased resistance to be overcome, on the mitral valves also ; and any one who has listened to the loud banging of the aortic valves during a uric acid storm (in migraine, for instance) will have no difficulty in realising what I mean. So that the valves of the left side of the heart are most exposed to injury by friction and percussion, just at the very time when there is an excess of the irritant uric acid in the blood ready to be precipitated upon them should the heat of action cause them to lose for a time their normal alkalinity.

And once a spot has thus become invaded by uric acid the irritation is always liable to be kept up and repeated until a serious and extensive lesion has been produced.

We have then certain conditions to which the fibrous tissues

of the heart are liable in common with all the fibrous tissues of the body tending to precipitate uric acid upon them, and we have certain other conditions which are common to the fibrous tissues of the heart valves and those of the joints. Can we wonder that these structures are so often affected in acute rheumatism at the same time, and doubtless the liability of the endocardium to friction, percussion, and strain, accounts for the greater frequency of endocarditis as compared with pericarditis.

With regard to the causes that determine the structures that will be invaded by uric acid, I will quote what Dr. A. E. Garrod (*loc. cit.*, p. 82), says as to the order of invasion of joints: "The influence of external causes in determining the seats of the lesions is far less conspicuous in rheumatism than in gout, but as has been already stated when rheumatic fever follows an injury the joint nearest to the seat of injury is usually the first to suffer."

Exactly so! the injury diminishes first of all the alkalinity of the affected structures, and then if the injury is sufficiently severe to cause general fever, the alkalinity of the whole body is diminished. The uric acid is first rendered insoluble near the injured structures (hence these are the first to suffer), and later on in other fibrous tissues of the body.

Dr. Garrod also says (same page): "Dr. Fuller has laid special stress upon the liability of joints which have been the seats of local mischief. Dr. Maclagan also regards strain as the most important influence at work in determining the seat of rheumatic lesions, and Dr. Peter Simpson and others have expressed their belief that the joints which are most exercised are specially liable to rheumatism. M. Besnier, who is inclined on the whole to agree with them in this opinion, does not think that the rule is sufficiently general for the establishment of a definite law."

There is no necessity to establish a definite law, but every one of the conditions here mentioned can be quite easily translated in terms of uric acid causation.

Joints that have been the seat of local mischief will contain a certain amount of fibrous scar tissue, which, as we know, is very lowly vascular, and this will easily have its alkalinity reduced and very slowly recover it again, and meanwhile uric acid will be accumulated and retained in it.

And the same argument will apply whether the local mischief was in the first instance due to uric acid or to external agencies. Once a scar has been produced uric acid will account for its continued irritation and progressive enlargement.

Thus, suppose a young woman has acute rheumatism, and a few pin point nodules are left on the mitral valves; she apparently recovers from her attack, and perhaps no murmur has been heard, but the valve, nevertheless, has been damaged to the extent of the above nodules, and these form microscopic scars, on which, however, uric acid will be again precipitated at the first opportunity.

And it may not have very long to wait, for, as I have said above (p. 154) every woman has more or less uricacidæmia at her menstrual period; and this by the high tension it produces may strain the mitral valve, diminish the alkalinity of the damaged nodules, and then, as the alkalinity is generally diminished at the end of menstruation clearing the blood of uric acid, and putting an end to the uricacidæmia, some of the urate in circulation may be precipitated upon the mitral valve, especially upon its damaged portions, and increase of lesion results.

And when this process is repeated month after month for years we can easily understand how a microscopic scar becomes at last a leathery and calcareous mass, and why a button-hole mitral is more commonly met with in women than in men.

We can also understand the connection which some have noticed between dysmenorrhœa and certain rheumatoid joint changes: for dysmenorrhœa means a more than usual fall of urea and acidity, a more than usually severe uricacidæmia, and consequently more severe and wide-spread irritation in the already damaged tissues of joints or valves.

So that these changes in fibrous tissues due to the irritation of uric acid are more liable to progress from small to great in women than in men, and are still more liable to do so in those women who suffer from dysmenorrhœa.

Before leaving this subject, I must quote what Dr. A. E. Garrod says (*loc. cit.*, p. 53) on the influence of sex: "Dr. Cheadle has called attention to the greater liability of girls to almost all the individual manifestations of the disease, and my own observations lead me to think with him, that not only chorea, but also subcutaneous nodules, erythema, and rheumatic

heart affections, are considerably commoner in female than in male children. It should be mentioned, however, that Hirsch found that rheumatic fever occurred more commonly in boys than in girls under the age of fifteen." From this latter statement we may, perhaps, infer that it is more common in girls after fifteen, when the menstrual influences I have spoken of come into play. In addition to this, the great activity in nutrition and metabolism, when at this time of life girls dash at one bound from childhood into womanhood, must affect the formation and excretion of urates, and greatly increase for a time the possibilities of acute rheumatism, and of uricacidæmia and its various results, and Dr. Cheadle says (*Lancet*, vol. i., 1889, pp. 824 and 871) that girls of 10-15 years old are twice as liable to rheumatic fever as boys of the same age. (See also chapter xii., pp. 249 and 253).

I quite agree with the authors quoted by Dr. Garrod, that the joints which are most exercised are specially liable, and believe that it is often possible to tell the occupation of the patients by observing the joints chiefly affected.

As regards physiology, the pains of rheumatism resemble, I believe, those of gout in being worse at night and better in the morning; that is to say, they correspond with the natural fluctuations in the uric acid excretion: though this may be often less conspicuous in rheumatism than in gout, as the former being an acute disease overpowers for a time the natural fluctuations: and in accordance with this the first symptoms may occur at very various hours.

The causes which appear to precipitate the attack are just those which would be certain to raise the acidity of the urine and diminish the alkalinity of the blood—thus a chill, getting wet through or sleeping in a damp bed; the excretion of acid from the skin is interfered with, up goes the acidity, a certain amount of uric acid is driven into the joints, this causes some fever, and the rise of temperature still further diminishes alkalinity and sends the uric acid into the joints.

Temperature in rheumatism at times resembles that of gout in being high at night and lower in the morning; at other times the highest point is in the morning. Of the temperature curves given by Dr. A. E. Garrod (*loc. cit.* p. 60) of rheumatic fever treated upon the expectant plan in fig. 1, the highest points are

in the evening, in fig. 2 they are for the most part in the morning, and in fig. 5 they are some in the morning and some in the evening though the morning, preponderates.

I think, however, that this is not very difficult to explain, for in rheumatic fever after the first start off (which is due to a very abnormal rise of acidity which may occur at any time, as it overpowers and obliterates the normal curves) the joints have their alkalinity very considerably diminished, and then the only effect of the alkaline tide or its representative will be to bring more uric acid to these joints where it is further rendered insoluble and retained, increasing the irritation in the joints, and so raising the temperature in the morning.

As to season. Acute rheumatism is not generally considered to present any definite relationships; and this is in accordance with what I have said, namely, that the attack is often the result of a severe cold or wetting, which may come at almost any season of the year, and that this interferes sharply with the action of the skin, producing a marked fall in general alkalinity which overpowers the natural curves; the only thing that is necessary for acute rheumatism to result is, that at the time of the wetting the blood should contain a considerable amount of uric acid, and this uricacidæmia would, for the reasons previously gone into (p. 15), be most likely to be met with in the spring and summer rather than in the winter, though severe exercise and perspiration would probably produce a temporary uricacidæmia at any time, hence the very serious effects of a wetting following close upon these conditions of muscles and skin. My friend, Dr. Eccles, read a paper at the West London Medico-Chirurgical Society (see *Lancet*, i., 1891, p. 1433) showing that exposure to cold and damp after fatigue, had important influence in the causation of rheumatic arthritis, and mentioned that his experience in over a hundred cases supported my views on the etiology of the trouble. And after what I have said about fatigue (p. 160), there should be no difficulty in completely understanding this sequence of causation. As regards experimental work, an arthritis resembling that of acute rheumatism can be produced without difficulty, or when present can be made worse or a relapse can be produced in exactly the same way and with the same drugs as in gout; indeed, as I have said, when one produces a relapse of gout by raising the acidity, the symp-

toms more often resemble those of rheumatism in that they affect several joints.

In my own person I have often produced symptoms which would, I have no doubt, have been pronounced rheumatism by anyone unaware of their origin.

And in hospital cases it is often quite easy to see how diet, weather, or other independent sources of inflammation produce a rise of acidity (diminished alkalinity) and cause a relapse or aggravation of the rheumatic symptoms. Thus I have related[1] how in a case under my care, a peridental abscess raised the temperature and produced a relapse of the rheumatism; and as I can now see, but did not understand at the time, the action of the rise of temperature was probably aided and abetted by the quinine which I gave for his dental troubles. (See "Action of Quinine," p. 21.)

The treatment of acute rheumatism by lemon juice (combined, by the way, with plenty of hot water, blankets, and other sudorific treatment) has been supposed by some to be an instance of the cure of rheumatism by the administration of an acid which would be strong evidence against uric acid causation.

But closer investigation hardly bears this out, for first of all, the lemon juice is given with copious draughts of hot water, and the patient is in bed wrapped up in blankets; so that the skin is kept active, and there is a considerable excretion of acids by this channel. Secondly, the effects of considerable quantities of lemon juice on the acidity of the urine is very slight and transitory, as I can vouch for from my own experiments. On several occasions I took either strong infusion of lemon in hot water, or strong doses of citric acid so far as I thought it safe to go (as citric acid in large doses is a powerful gastro-intestinal irritant), and the result as regards the acidity of the urine was very small; on one or two occasions taken from hour to hour, my curves show that it rose a little at first; but the effect on total acidity of the twenty-four hours was little or nothing, and where the lemon is combined with copious hot water and blankets, I have no doubt that the result is a fall of acidity and an increase of the alkalinity of the blood, which will account for the cures it

[1] Wood's "Medical and Surgical Monographs," February, 1890, p. 355.

has been said to effect in some cases. On this point Dr. A. E. Garrod says (*loc. cit.*, p. 200) : " Dr. Fuller, on the other hand, found lemon juice do good in only three out of a series of twenty-nine cases, and ascribed to it the production of depression, griping, and diarrhœa."

If it produces griping and diarrhœa this would bring about a fall of acidity of the urine, and an increase of the alkalinity of the blood, and might in some cases be of use in this way, just as a drug about which I have previously written and which has been more in favour for the treatment of rheumatism than lemons, namely colchicum.

Dr. A. E. Garrod says (*loc. cit.*, p. 201) : " The extensive employment of colchicum in the treatment of acute rheumatism was doubtless owing to the supposed intimate relationship of rheumatism and gout." My own experience of colchicum showed that it produced considerable intestinal pain and irritation, and as the result of this a fall in urea and acidity, and the falling acidity brought about a plus excretion of uric acid. It should, therefore, according to my rule, be useful in all arthritic trouble which is due to uric acid. About its value in gout there is no dispute, and it is interesting to note, as I have previously remarked, that some have considered that in gout, where it fails to purge, it fails to do good, which is in favour of my argument. In rheumatism it has been next to salicylates and alkalies, one of the best known treatments, and if I am correct, it really acts as an alkali in the way I have mentioned.

About cinchona and quinine opinions are divided, but combined with alkali Sir A. Garrod, Sir Dyce Duckworth, and others are in favour of its use. If it is given with sufficient alkali to keep the urate in solution I think it may do no harm, though its action is as I have said to produce considerable uric-acidæmia; where there is much urate in the spleen, and especially where the spleen is large; and where it produces such uricacidæmia there would probably be considerable headache as its result.

Of alkalies Dr. A. E. Garrod says (*loc. cit.*, p. 203): " The alkaline treatment renders the highly acid urine neutral or alkaline, without causing any increase in its quantity. The blood is found to coagulate more slowly, and the frequency of the heart's beats is considerably diminished." The reason why

the urine is not increased and why the heart's beats are diminished is not, I hope, difficult for anyone to understand who has read my previous chapters, and I regard these as conclusive signs that the alkali has produced considerable uric-acidæmia, which, under the circumstances, we should expect, and Dr. Garrod goes on: "But the chief claim of this treatment was that it diminished the liability to cardiac implication, and in support of this claim the statistics of Drs. Dickinson, Senator, Chambers, and others may be quoted, all of which show a considerably smaller proportion of cases with endocarditis and pericarditis among patients treated with alkalies than amongst those treated by other methods."

A similar claim has now been made for salicylates by Dr. Mitchell Bruce[1] and others, and if the cardiac troubles are due to uric acid it is easy to explain the action in both cases, but it seems to me that no other rational explanation has as yet been suggested. Both drugs have the same action on uric acid, but otherwise they have little in common.

As regards the treatment by salicylates, I have pointed out that the excretion of urate during the first few days of their use in acute rheumatism is enormous, that the excretion is not only absolutely large as 26 grs. in the 24 hours, but that uric acid bears an abnormally large relation to the urea excreted along with it, as 1-17 in the case which excreted the 26 grs. and 1-14 in the case of a boy of 14 also under my care (see fig. 35.)

This figure shows an enormous excretion of urate in the first 24 hours in which salicylate of soda was taken, the absolute quantity being upwards of 26 grs., but taking urea as our standard only 16 grs. of urate were formed on this day (in the relation 1 to 35.) Therefore about 10grs. of urate came from some source other than formation, and probably it was this urate which caused the arthritis, and with its removal and excretion under salicylate there was a marked fall of temperature and amelioration of all the symptoms.

With regard to November 8 the excretion of six hours of the alkaline tide period (all that could be got before treatment) was multiplied by four and counted as a day. This accounts for the slight plus excretion of urate and the low acidity. If the whole

[1] *British Medical Journal*, 1890, vol. i., p. 941.

24 hours could have been collected urate would, no doubt, have been far below urea and acidity much higher.

On November 10 the urine was lost by mixture with another specimen, and on November 11 we see that urate is below urea in spite of 80 grs. of salicylate in the 24 hours. Most of the available urate had been removed on the previous days, and it had nothing to act upon, but with this the temperature is normal and the patient convalescent, and next day he wants to get up.

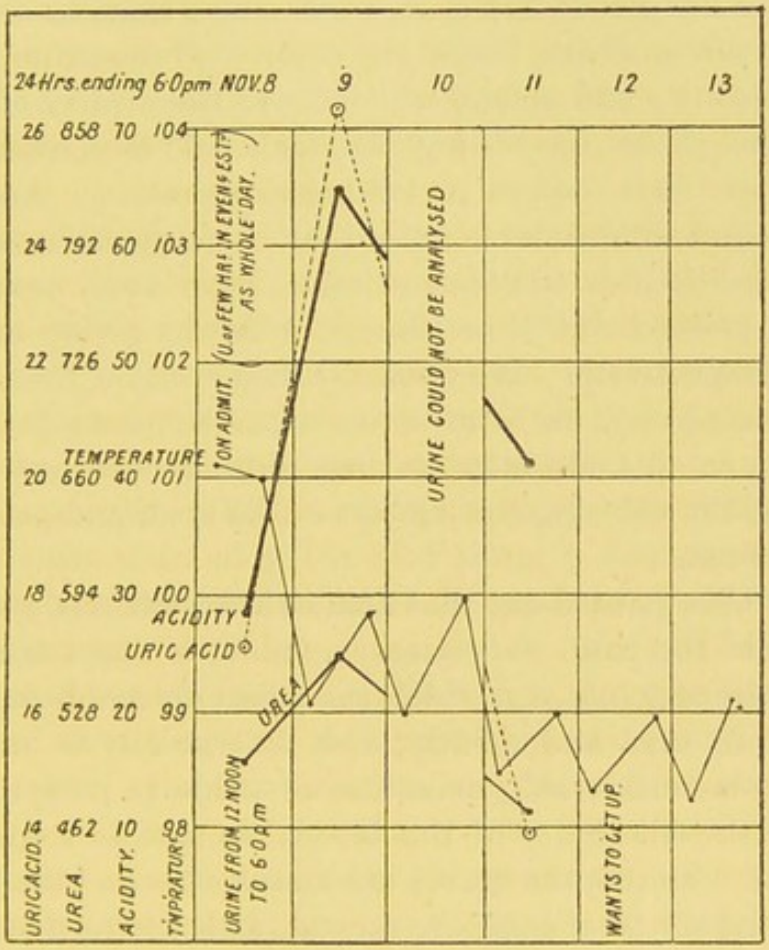

FIG. 35.—CURVE OF EXCRETION OF URIC ACID IN ACUTE RHEUMATISM, ON SALICYLATE OF SODIUM.

Compare this with the excretion of urate under salicylate in physiological conditions (fig. 4, p. 20). The curves are seen to be very similar. The only difference is in the absolute quantity.

Now, in accordance with my premiss that uric acid is never formed in greater proportion to urea than 1 to 35 (see my facts and deductions in chapters ii. and iii.), in both the above cases about half the uric acid excreted under salicylate must have come

from some source other than the formation of that day, and I have suggested that this extra urate came from the joints, and that its removal accounted for the subsidence of the pain, irritation, and temperature, and as I have also pointed out the value of the salicyl compounds in acute rheumatism is proportional to their power of dissolving and eliminating uric acid. (*Medico-Chirurgical Transactions*, vol. lxxiii.)

I have also pointed out that acids do harm in acute rheumatism, and that cases so treated take a longer time to get well than those which are given only mint water; also that, as observed by others, ammonia which keeps the acidity of the urine high does harm, while soda and potash which lower the acidity of the urine do good, and if we are dealing with uric acid as a cause of rheumatism these facts require no further explanation. An arthritis practically indistinguishable from that of acute rheumatism, and an endocarditis also indistinguishable have been produced, as previously pointed out (*Practitioner*, 1891) by giving and injecting acids respectively. We must not forget either that, as Sir A. Garrod has shown, urate of ammonium is insoluble, and that ammonium compounds may act like those of lead, mercury, and other metals in clearing the blood of uric acid, and precipitating it on the joints.

I have also pointed out that acute rheumatism is a self-curing disease, that the pain, sleeplessness, failure of appetite and digestion, and the absolute rest which the pain enforces bring about at last, a fall in urea and acidity, and that acidity is still further reduced by a considerable excretion of acids in perspiration; so that when the alkalinity of the blood has thus to a considerable extent been restored, the urates are dissolved out of the joints and excreted, and the fever comes to an end, with the production, however, of considerable uricacidæmia, anæmia, and debility (p. 251).

More or less headache and slow high tension pulse are the common signs of this uricacidæmia, and Dr. A. E. Garrod (previous reference, p. 64) gives traces of such a pulse, while, as I have previously pointed out, Dr. Stephen Mackenzie says migraine alternates with acute rheumatism, and he deduces from this the suggestion that both diseases are nerve storms; but I think that my remark about Jupiter in the chapter on "Gout" will apply again here.

In pathology, acute rheumatism may be produced by any-

thing that produces a sharp rise of acidity or fall in the alkalinity of the blood at a time when there is a considerable supply of urate in the circulation (uricacidæmia), but if there is no urate a rise of acidity may produce little or no effect, hence those who eat most meat (see Bouchard[1]) and drink most beer, and have in consequence most uric acid stored in their body, will be most likely to have occasionally considerable uricacidæmia, and when exposure to cold and wet, or the sudden onset of any fever supervenes upon this, acute rheumatism may result.

Now tonsillitis is very commonly a forerunner of rheumatism, and indeed some have claimed it as a part of the rheumatic process, but if this is the case it must often be its only sign, as there may be no other symptom of rheumatism either before or after it.

But tonsillitis is, in my experience, very often associated with conditions of fatigue and over-exertion, and these are just the conditions which might bring about considerable uricacidæmia (see chapter viii.), and when tonsillitis with fever supervenes upon this, it is hardly to be wondered at that we should have some joint pains or even acute rheumatism.

Influenza again, with its rapid rise of temperature, generally produces some pain in joints and fibrous tissues, and several cases have been recorded in which it has also produced endo- or pericarditis.

A fever, however, has a double action, for supposing that at the time of its onset there is no uricacidæmia, it will not produce any rheumatic symptoms, but as the fever rises the acidity of the urine rises also, and the alkalinity of the blood is diminished, the excretion of uric acid falls below formation, and while the fever lasts a considerable amount of it may be held back in the body, in the liver, spleen, and elsewhere; and when the fever comes to an end and the acidity falls, more or less uricacidæmia will result from the washing out of this stored uric acid. On this let us suppose there supervenes a sharp rise of acidity (from diet, exposure to cold, or the inflammation of any organ occurring as a complication), and acute rheumatism of more or less severity may be the result; this is to my mind the explanation of the rheumatism that follows scarlatina, and may follow other fevers, as measles (see Sansom, quoted by Dr. A. E. Garrod, p. 182, and

[1] *Leçons sur les Maladies par Ralentissement de la Nutrition*, p. 241.

paper read at the Royal Medical and Chirurgical Society on "Measles as a Cause of Endocarditis," see *Lancet* i., 1891, p. 880), and compare this with my remarks on the effects of measles on the urine in a case of morbus Brightii, p. 277. The rise of acidity in the fever which cleared the blood of uric acid might, under certain conditions, have driven that urate into the fibrous tissues of the joints or heart; the clearing up of the uricacidæmia allowed the arterioles of the kidney to relax and profuse diuresis and removal of anasarca resulted. We here, perhaps, see the relationship of nephritis with the chronic uricacidæmia which so often accompanies it, to the disease of the aortic valves, which is not rarely found along with it in the *post-mortem* room. (See Dr. Norman Moore, *St. Bartholomew's Hospital Reports*, 1887, pp. 290 and 291), though no doubt the high blood pressure of the uricacidæmia will directly strain the aortic valves.

There is, I think, evidence to show that the acids of beers and wine, and the excessive formation and introduction of urates in a highly nitrogenous diet play much the same part in rheumatism that they do in gout, only in acute rheumatism where the onset is violent, and the sharp rise of acidity is probably due to the action of several causes working concurrently, it is difficult to apportion to each its actual share in the result; but it is well-known to be dangerous to give meat, beer, &c., too soon after an attack, and the way in which they tend to produce a relapse is now, I hope, obvious.

And in not a few cases of rheumatism, just as Sir A. Garrod observes to be the case in gout, the effect of giving iron is very promptly to bring about increase of pains and rise of temperature, and in a patient suffering from anæmia recently under my care, who had had acute rheumatism, it was found to be quite impossible to give iron on account of the rheumatic symptoms it produced, and in several cases of what appeared to be chronic rheumatoid arthritis I have had to give up the administration of iron for the same reason, and if the joint symptoms in these cases are due to chronic irritation by urates there is no difficulty in understanding the facts.

Age is a very important point, because it furnishes probably the chief causes of the differences between gout and rheumatism, and I have already pointed out that the condition of the joints is probably very different in the young and in the old.

Sir A. Garrod has shown that the tissues of joints are not only less vascular, but are less alkaline than the blood and other tissues, and there can, I think, be no practical doubt that as life goes on, as the arteries become tortuous and degenerate, and as activity of mind and body lessens, the circulation in these joints becomes less and less well maintained, and their alkalinity is not only continually reduced, but slighter and slighter causes will suffice to render them neutral or even acid, and it is this sequence of events probably more than any other which produces the stiff and painful joints so common in the aged, even where no rheumatoid changes are obvious.

So that while the joints of the young are both more alkaline and are better able to maintain their alkalinity, this may, nevertheless, be overcome by a great and general fall of alkalinity, which affects many joints at once, and is due to a powerful external cause (acute rheumatism).

In the old, on the other hand, the joints are less alkaline, and have little power of maintaining it; comparatively trivial external causes (a slight injury, a little extra exertion, cold, &c.) may diminish the alkalinity of a given joint, especially those of the hands and feet when the peripheral circulation is feeble, and gout results.

And it is extremely probable that uricacidæmia itself may by contracting the vessels render the circulation in the extremities less active, and so aid in diminishing the alkalinity of certain peripheral joints, in which the uric acid from the blood is eventually collected and deposited.

But age has important influence on another factor of uric acid arthritis, namely, the absolute quantity of uric acid that is formed, for while in adults urea is formed in about the proportion of three or four grains per pound of body weight per day, and uric acid in its natural relation of 1 to 35 would be about .09 to .11 gr. per pound per day, in a child of 3 or 4 years old urea may be as much as 9 or 10 grs. per pound, and uric acid .27 to .3 gr. per pound.

A child or young person is thus by nature placed much in the position of an adult who eats largely of meat. The daily formation of uric acid is large, and uricacidæmia and the arthritic irritation which depend on formation for supplies are correspondingly easily produced.

It is little wonder then that when young persons who have naturally this extensive nitrogenous metabolism, increase it by eating largely of meat, meat extracts, juices, and essences, the introduction and formation of uric acid should be very great, and the possibilities of resulting mischief considerable, and that, as pointed out by Bouchard (previous ref.), children fed on meat and meat extracts should often suffer from gastro-intestinal derangements, skin diseases (see chapters x. and xi.), and early migraine (uric acid headache), and that rheumatism and its most serious manifestations should come early.

It seems to me that if I have escaped from migraine (uric acid headache), by reducing my nitrogenous metabolism, and the introduction of uric acid, it is no very extraordinary thing that children whose naturally large nitrogenous metabolism has been increased by inordinate indulgence in meat should suffer severely, and the facts carry their own moral.

Age also influences one or two minor points, which, however, may at times have considerable power in precipitating rheumatic (uric acid) arthritis.

One of these is the fact often insisted upon by a teacher of whom I have the most kindly recollections, the late Professor Rolleston, of Oxford, that small animals have necessarily much more surface in proportion to bulk than large animals; for surface increases as the squares, but bulk increases as the cubes of the dimensions. Hence external influences, such as wet and cold, will have proportionally much greater effects on small than on large animals, and wet and cold, as we have seen, raise the acidity of the urine, and diminish the alkalinity of the blood by checking the excretion of the skin (Garrod), and it follows that rises of acidity from this cause will be greater and more powerful in the young than in the old.

Another point is that in children and young persons (probably in consequence of their more active metabolism) slight disturbances will produce great increase of temperature, and rise of temperature means, as we have seen (pp. 60 and 153), rise of acidity, the two things (fever and acidity) being probably co-resultants of increased metabolism. While the extraordinarily rapid development of girls at the age of thirteen (p. 249), may quite account for their liability to acute rheumatism about that age, as well as to chlorosis and anæmia a few years later.

Young persons then are, from the action of natural causes, often liable to have considerable uricacidæmia, and whenever external cold or slight febrile disturbance supervenes upon this a powerful rise of acidity will drive the uric acid out of the blood into the joints and other tissues, for these tissues no doubt share largely in any general fall of alkalinity.

A child with gastro-intestinal disturbance and loss of appetite, has a headache and slow pulse, the signs of uricacidæmia. On this there follows exposure to cold and wet, a slight sore throat, a peridental abscess, or other cause of febrile movement, and the resulting fall in alkalinity quickly produces a multiple arthritis with endo- or pericarditis, and changes the picture to that of acute rheumatism.

In this way the production of acute rheumatism may be completely accounted for by the action of causes that are to be met with every day, and the wonder is that any children should escape an attack, but it is fortunately necessary that a good many causes should act together, and this can only occasionally be possible.

Thus uricacidæmia means a large excretion of urate, and where this has gone on for several days the amount in circulation will be reduced. Again, gastro-intestinal disturbance means diminished metabolism and lessened formation of urate, so that unless external cold or febrile movement supervene at an early stage there will not be enough urate to produce the most severe effects on the fibrous tissues.

If I were to describe cases in illustration of even a small number of the points I have mentioned, I should have to increase this volume to a ponderous size, the opening of which might be regarded as a serious matter. I intend it, however, as a mere outline of which the details can be filled in later.

I shall, however, break through my rule here to the extent of quoting three cases which were under the care of Dr. Savill, at the Paddington Infirmary, and the notes of which he has very kindly placed at my disposal, as they illustrate several of the most important points I have mentioned.

I.—John G., age 69, coachman. Admitted February, 1886. Rheumatism and gout very badly for years in knees and ankles. First severe in 1853, in right hand, then in feet, and then general. Father asthma and slight rheumatism, died at 82 years of age.

On admission, February, 1886 :—

Urine 1018. No albumen.

March, 1886.—Much better, gets about fairly well, is taking cod-liver oil.

April, 1886.—Urine 1020. Cloud of albumen.

October, 1886.—Left hip painful, 2 in. shortening and joint disorganised.

November 30, 1886.—Giddy and headache in morning two or three days ago ; better now.

December, 1886.—Much pain in hip. Hands show marked rheumatoid change and distortion of fingers.

1887.—Much the same, giddy on exertion. Pulse compressible, arteries thick. Urine 1008. Trace of albumen.

1888.—Many joints affected ; marked rheumatoid changes in hands, elbows, shoulders, knees, and left hip.

1889.—Urine occasional albumen, joints somewhat relieved by soda baths.

1890.—Pains vary with weather, and are worst in east wind. Can walk with the aid of a stick.

August, 1890.—Urine 1014. Albumen $\frac{1}{6}$. Anasarca of both legs, petechiæ on right.

November, 1890.—Pulse tension plus. Urine 1016. Petechiæ on both legs.

January 6, 1891.—Urine 1012. Alb. large trace.

January 30.—Diarrhœa and collapse. Died 9.15 p.m.

Post-mortem Notes. — Body exceedingly well nourished. Rigor marked. Petechiæ on legs numerous.

Heart.—17 oz. Left ventricle large, valves normal. Atheroma of abdominal aorta. Arteries tortuous and thick.

Lungs.—Emphysema and congestion.

Liver.—40 ozs. Hobnail cirrhotic.

Kidneys.—$2\frac{1}{2}$ ozs. each. The right contains a cyst as large as a hen's egg.—Cortex much reduced. Capsule adherent, surface granular.

Spleen.—5 ozs., capsule thick.

Joints.—Deposit of urate of soda in cartilage of metatarso-tarsal, and metatarso-phalangeal joints of right great toe.

We may sum up the *post-mortem* by saying gout with extensive rheumatoid changes, granular kidneys, cirrhotic liver, hypertrophied heart, and degenerate vessels.

II.—Charlotte W., age 62, laundress. Clinical paper headed "Progressive Chronic Articular Rheumatism."

Father died at 70 of rheumatism.

Mother died at 68 of asthma.

Patient had rheumatism first in toes, then in ankles, and then knees.

Admitted July, 1888. An anæmic woman, with enlargement of second phalangeal joints affecting the bone ends. Metacarpo-phalangeal joints also enlarged. Some tilting of fingers to ulnar side.

Left knee much enlarged; very tender on the inner side; brawny œdema of lower part of joint.

Heart.—Systolic murmur at apex and left base. Pulse 90. Artery thick, tense, tortuous.

August, 1888.—Pulse trace to-day shows a large first wave high up in the trace.

Urine, albumen $\frac{1}{7}$.

Bullæ forming on ankles.

September, 1888.—Cough and dyspnœa, increasing. Died on 21st.

Post-mortem, September 22, 1888.

Body somewhat emaciated, rigor absent.

Heart.—18½ ozs. Left ventricle hypertrophied. Aortic valves incompetent, with thick attached borders. Mitral valve slightly thick.

Lungs.—Contain infarcts, with general congestion and œdema.

Kidneys.—Numerous cysts, small, hard, granular. Right 3 ozs. Left 4 ozs.

Liver.—57 ozs., nutmeg with fatty degeneration.

Joints.—Copious deposit of urate of soda, much erosion of cartilage, tissues around thickened and infiltrated with deposit.

This, then, is another case of gout with extensive rheumatoid changes (diagnosed during life as "Progressive Chronic Articular Rheumatism") granular kidneys, but to these are added disease of aortic valves, and the condition of the lungs and liver was no doubt secondary to this.

III.—Mary C., aged 65. Dressmaker. Admitted January, 1890. Case headed "Progressive Chronic Articular Rheumatism," with gouty history.

Father delicate, suffered from rheumatics in early life.

Mother and one sister died of diabetes.

One brother has rheumatism.

One brother has gout.

Patient had inflammation of the kidneys when a girl, and in 1885 an abscess in the face, which discharged for thirteen months.

The rheumatics came on twenty-seven years ago when she was pregnant, and got worse after her confinement. First came in her ankles and feet.

Did not finally give up work till eight years ago.

Is now able to get about on crutches.

Present condition.—Metacarpo-phalangeal joints seem most thickened and distorted, and their movements are very limited. But all the joints, elbows, knees, ankles are thickened and distorted, and more or less fixed. Ankles seem to be completely so.

Hips and shoulders least involved.

Spine movements impaired.

Skin pale and smooth, not glossy. No fluid in any joint.

Heart sounds normal, but feeble.

Lungs emphysema, but natural otherwise.

Urine normal.

March, 1890.—Gets more helpless.

May, 1890.—Urine pale, cloudy, acid, 1028. No albumen.

August, 1890.—Lin. terebin relieves pains.

December, 1890.—Great pain in right arm.

Urine 1022.—Acid, cloudy. No albumen.

March, 1891.—Suffers a great deal from pains, but they are lessened by lin. terebin.

May, 19, 1891. Face pale. Pain between shoulders and across abdomen. Breathing laboured. Bronchitic sounds front of chest. Bronchial breathing over right upper lobe, and crepitations on both sides of back.

Sputum thick, purulent, not rusty.

Slightly better the next day (May 20), but there is bronchial breathing all over left back now.

She died on May 24.

Post-mortem, May 26.—Pleuræ a few old adhesions both sides.

Heart.—12 oz., substance firm. Aortic cusp of mitral valve slightly thick.

Lungs.—Right 22 oz. Left 23½ oz. Considerable consolidation.

Liver.—Pale, fatty, 40½ oz.

A few small gall stones in bladder.

Kidneys.—Each 4 oz. Cortex a little diminished. Capsule peeled fairly easily, leaving a somewhat roughened surface.

Joints.—Left great toe. Cartilage eroded. Cancellous tissue exposed. No urate deposit. Left knee similar changes. No urates. Metacarpo-phalangeal joint of right index finger in same condition as great toe.

Here we have extensive rheumatoid changes affecting the same joints in same way as in the previous cases where urates were found, but there are no urates. Kidneys slight fibrous changes. Heart not markedly hypertrophied. Death from pneumonia.

Here then we have three most interesting cases, all diagnosed during life, as chronic rheumatoid arthritis or chronic progressive rheumatism. In two of them urates are found in the joints after death. In the third none.

Now, according to ordinary pathological nomenclature, the first two cases would be called gout, and the third rheumatoid arthritis, but during life they were indistinguishable. There is then some confusion of ideas between clinical medicine and pathology.

I think, however, that my knowledge of the solubility of uric acid enables me to clear up the matter.

From my point of view the joint changes in all three cases were the work of uric acid, but in one of the cases after it had set up the mischief which ended in the more or less complete destruction of joints, it was got into solution and passed in the urine, so that at the *post-mortem* none was left in the joints; in the other cases, no doubt, a good deal of urate had been passed in the urine, and if the patients had lived a little longer none would have been found in their joints either, and all three cases would have been called rheumatoid, which is absurd.

It will be observed that the case in which there were no urates differed from the others chiefly in this, that she was much more crippled by her disease than they were. We are told that she had done no work for eight years before admission, and when in the infirmary for the last year or eighteen months of her life her joints were so stiff and fixed that she was practically bedridden.

Now, the effect of this helpless condition would be to diminish metabolism. Urea and acidity of urine would steadily fall, the

alkalinity of the blood, and therefore its solvent power over uric acid, would increase, and excess of uric acid would be excreted so long as there was any in the body to be got into solution. The liver and spleen would first be cleared, and then gradually during weeks and months the urates in the joints would also be got into solution and passed out in the urine.

See also *Lancet*, vol. ii., 1893, p. 133, case of obesity previously quoted, in which a similar failure of the power to take exercise explained the departure of gout and its absence in spite of a liberal animal diet.

Excessive excretion of uric acid was no doubt occurring in the other cases also, as metabolism was probably low in all; but in these cases the plus excretion had been less marked or less continuous, and some urate was left undissolved at the time of death.

It will be seen that Case I. had well-marked granular kidneys, and yet the specific gravity of his urine was, on some occasions, as high as 1018 or 1020. I have very little doubt that on these occasions he was excreting an excess of uric acid, which raised the specific gravity of his urine in spite of his having granular kidneys.

I will just mention a case I was fortunate enough to see in the *post-mortem* room of St. Bartholomew's. It was that of a man, aged 41, who had extensive joint-troubles with granular kidneys, endo- and pericarditis. Of his joints, some had urate and others none; thus there were rheumatoid changes in both knees and both elbows, the right ankle, and the right great toe, and there were urates in both elbows, the left knee, and the right great toe. Sir Dyce Duckworth, who was looking at the *post-mortem*, said that seen apart these joints might be called gouty, and those rheumatoid.

This man also had granular kidneys, and if I may trust my memory this had not been diagnosed during life because the specific gravity of the urine was too high, doubtless this was due to an excessive excretion of urates which would have been found if the urine had been examined.

The amount of urate was probably from the action of various causes, not exactly the same in any of these joints to start with, and when the alkali began to act and remove urate equally from all, the result was that some were cleared before others,

for if equals be taken from unequals, the remainders are unequal; hence some joints contained a little urate, others none.

We thus see that the "intimate relationship of rheumatism and gout" is not a supposition but a fact, and a fact founded upon community of causation. That some very simple facts with regard to the solubility of uric acid will enable us to explain all the phenomena and symptoms of both diseases, and lastly, that the failure to find urates in the joints after death is no proof that they have not been there, and produced or assisted in producing the lesions of cartilage and fibrous structures which are found.

The chief point in the treatment of all uratic arthritis, whether it presents the clinical picture of gout, rheumatism or rheumatoid arthritis, is the removal of the urate, and the more acute the symptoms the more important is this indication.

When, however, all the conditions are chronic, when there is little or no temperature, and the pain is remarkable rather for its extent than its intensity, and when drugs like iron can be taken without markedly increasing the pain, the removal of the urate has already probably to a large extent been affected by nature, and the indications are then rather to treat the damaged structures it leaves behind.

The first indication is met by salicylates, or, if there are good reasons for not using them, then by alkalies.

The salicylates must be given in a sufficient dose, because, other things being equal, the amount of urate eliminated depends on the amount of salicylate in the blood to combine with it. I have seen gr. x. of salicylate of soda given three times a day in acute rheumatism without the smallest effect, when gr. xx. every two, three, or four hours promptly relieved.

There are but few reasons for not giving a good dose, the head symptoms they produce are generally trivial, and in albuminuria and Bright's disease there is but small evidence that they really increase the albumen.

If they do cause a little depression, what is that to the depression of a prolonged attack of acute rheumatism? And it seems that a large part of the depression they have been credited with is really due to impurities, which we are gradually learning to eliminate. (See an interesting article by Dr. Lees, *Lancet*, vol. ii., 1893, p. 190.)

The second indication requires nourishing food, perhaps wine, cod-liver oil, and alteratives such as iodides, arsenic, &c., which possibly affect the circulation in the damaged structures, and locally blisters, massage and electricity.

Then there is one indication which is common to both conditions, namely, to keep as low as possible both the introduction and the formation of uric acid, and of this I shall have to say a good deal in the following chapter.

But if there is anything in what I have suggested as to the causation of those diseases, if there is any truth in the observations of M. Bouchard which I have quoted, we ought to be able to prevent these troubles, and I, for one, believe that we can.

And a hint of something of this kind is intended, I think, to be conveyed in the following passage from the very interesting address on medicine delivered by Dr. Drummond at Newcastle (see *British Medical Journal*, vol. ii., 1893, p. 300), where he is reported as saying: "Would a substantial reduction in the number of chronic heart cases as the result of the recognition of the fact that many are due to curable and preventable causes which an early and successful treatment might reasonably be expected to subdue, be a dream too visionary for us to indulge in? I think not; but assuredly until we fully appreciate the causes, a dream it will remain."

I believe that if the children of rheumatic or gouty families can be placed early in life on a diet which reduces as far as possible the uric acid directly introduced, and at the same time reduces so far as is compatible with healthy nutrition, the formation of uric acid in their bodies, such children, in spite of their inheritance, may never suffer from either disease. I shall never lose an opportunity of doing this, and would strongly urge others to do the same, for this change of diet which promises so much can, as I shall endeavour to show in the next chapter, be effected without any damage or risk.

I further believe that those who have suffered from these diseases, whether they have damage in joints, endocardium or other fibrous structures, can to a very large extent prevent their damage going further, by a similar change of diet continued for the rest of their lives. I have been acting on this principle for several years, and have, I think, every reason to be gratified with the results, some of which I have mentioned.

We must bear in mind also the active metabolism in children, and the fact that they form much more urea and uric acid per pound than adults, and this makes it all the more important to do nothing to stimulate nitrogenous metabolism, and not to introduce a single grain of uric acid that is not necessary. It is not, however, uncommon to find that mothers of such children are in the habit of dosing them with beef-tea because they do not care for meat, and thus Nature's effort to protect them is nullified.

CHAPTER XVII.

Treatment.

The diseases treated of in the first fourteen chapters are more or less directly due to excess of uric acid in the blood, those in the fifteenth and sixteenth are due to this excess of uric acid being driven out of the blood into certain fibrous tissues. The diet treatment of these diseases is the keeping the body and blood free from an excess of uric acid, and we have now to consider the way in which this can be done.

Now, uric acid is met with in excess in the body and blood chiefly, as we have seen, from two causes: (1) that it has been introduced in excess by the consumption of articles of food which contain it or other members of the xanthin group, such as meat, or fish, or tea, coffee, cocoa or guarana; or (2) because so much nitrogen is taken that the uric acid formed out of it in the relation to urea of about 1 to 35 is owing to the high acidity which the salts and other products of nitrogenous metabolism produce, not all excreted, and a store is gradually formed in the body to the extent possibly of from 50 to 400 grains in a year.

Speaking of guarana reminds me that it is probably by its nitrogenous or xanthin elements that it cures sick headache (uric acid headache), because strange as it may seem at first sight, a dose of uric acid itself will cure a uric acid headache, and as we have seen in chapter iii., the first effect of a dose of uric acid, and probably also of ammonia and nitrogen in other forms, is to raise the acidity and clear the blood of uric acid; and I remember years ago, before I began to study medicine, pointing to a big plate of meat in front of me, and saying, "My

headache will be all right when I have eaten that." I now know that the nitrogen and salts so introduced raised the acidity of the urine, reduced the alkalinity of the blood, and cleared it of the uric acid that was causing my pain. But I would earnestly warn any fellow sufferer against treating his trouble in this way, for I believe it to be a most dangerous course; the uric acid thus cleared out of my blood was not cleared out of my body, and in addition more was introduced, and for years afterwards I suffered from most terrible headaches, while the urates thus stored up were passing through the blood, and I believe that damage was then done to my heart, vessels, and other structures, which no subsequent change of diet has sufficed to wipe out.

I would say, further, do not under any circumstances resort to caffeine or guarana for relief; they are practically uric acid, and present relief is obtained at the price of future suffering, and I have seen several cases in which the employment of these substances for some considerable time for the relief of headaches, &c., has been followed by very deplorable consequences.

With regard to diet, we can give the main point in very few words, for we have seen that as flesh diet increases the introduction of uric acid, it increases the formation of uric acid, and its salts diminish the excretion and elimination of uric acid. A milk and vegetable diet, on the other hand, introduces less uric acid, causes the formation of less uric acid (because urea is not unnecessarily high), and its salts promote the free elimination of all uric acid that is introduced into or formed in the body. Thus we see (p. 9), that I excrete now 11.1 grs. of uric acid, of which 9 grs. are formed in the body, and 1.8 grs. are introduced ready formed, while a fraction of a grain is accounted for by the excretion of urates previously stored in my body. With this low formation and introduction of urates I have but rarely any excess in my blood, and consequently suffer little or not at all from headache.

In former years on ordinary diet I used to excrete 500 to 600 grs. of urea, and in the above proportions I must have formed 14-17 grs. of uric acid and introduced from 3-4 grs. ready formed in my food. It is easy then to see why I often had an excess of urates in my blood, and frequently suffered from the effects of such excess, namely, high blood pressure, headache and

mental depression. Further, I believe that the section of mankind that lives to eat may possibly introduce as much as 2 grs. of uric acid with each meal, or 6-8 grs. in a day or more, and sooner or later will suffer in proportion.

We can now quite understand why in Persia, where only the rich eat meat, gout has come to be known as the rich man's disease (see *Proceedings of the Royal Medical and Chirurgical Society*, third series, vol. v., p. 46, where this interesting fact is contributed to the discussion on my paper on the iodides by the physician to the Shah), and we have already seen on page 251, that the children of the rich are in this country specially liable to anæmia, no doubt due to excess of meat in their food, and in chapter xvi. we have seen that M. Bouchard considers that children thus overfed are liable to many troubles, including migraine and acute rheumatism.

We have, then, two things to do to attain our object: we must cut off all food which contains much uric acid, and which is not absolutely necessary; and we must diminish the total income of nitrogen so that much uric acid shall not be formed in the body, and we must keep the acidity from rising too high, so that all the uric acid which is formed may easily and at once pass out in the urine, and not accumulate and form a store in the body.

With regard to cutting off we may, I think, at once forbid tea, coffee and cocoa, or permit them only in the smallest possible quantities as flavourings. We may cut off at once such animal food as contains much uric acid, and give only so much of the less harmful kinds as is necessary for nutrition.

This raises at once two questions:—

(1) What animal foods contain much uric acid ?

(2) How much animal food is necessary for nutrition;

I can answer neither question completely, but I must nevertheless attempt to do what I can, and hope that further knowledge, when we attain it, will not show that I have been very far wrong.

There can be very little doubt after what I have said, that the best answer to our first question is to be obtained by the physiological test which I have used in the case of meat. (See p. 66, and *Journal of Physiology*, vol. xv., p. 168.)

That is to say, when a person is on a practically constant diet, and is watching his uric acid and urea excretion from day to day,

if the taking of a known quantity of some substance, such as fish, or meat, always without exception increases the excretion of uric acid out of proportion to urea, such substance probably contains an excess of uric acid which it introduces into the blood, and should consequently be as far as possible avoided by those who suffer from uricacidæmia.

Such a physiological test is much more valuable than any mere estimation of the urates contained in meat can possibly be, for though we may pass it through a mincing machine and make an extract of it and estimate the uric acid it contains, this will carry us but a small way, for many animal tissues contain other members of the xanthin group besides uric acid, and these, as we have seen (p. 68), are apparently converted into uric acid, when introduced into the human body. (See also p. 360.)

I will now give a few figures showing the quantities of uric acid I have found by extracting some of the animal tissues commonly used for food.

Substance.	Uric Acid per cent.
Lamb (cold roast leg)	.050
Soup (made from bones)	.0068
,, (made from meat)	.0202
Hospital beef tea	.0980
Saddle of mutton	.020
Mutton (cold roast leg)	.016
Veal (cutlet)	.049
Beef (cold sirloin)	.016
Kidney of sheep	.049
Liver ,, ,, ...	.091
Fowl (breast)	.024
Rabbit	.015
Mackerel	.032
,, (boiled only ¼ of an hour)	.015
Plaice	.0039
Herring (fresh)	.0040
,, (Loch Fyne, kippered)	.0900
,, (bloater)	.031
[1] Beef-steak (treated raw)	.019
[1] Meat juice	.697
[1] Meat extract	.883

They were estimated as cooked and ready for eating, except as mentioned.

[1] These are from p. 49, placed here for comparison.

We see from this that young meat (lamb and veal) contains more than old (beef and mutton), and that as we should expect soup made from meat contains considerably more than soup made from bones. We see also that the kidney and liver of sheep contain considerably more than their muscles, just as is the case in man, and some kinds of fish appear to contain a considerable quantity even more than meat, and any increase in the fish taken has certainly appeared to me to markedly increase the amount of uric acid passing through the blood, but I intend to repeat this physiological test again more carefully.

The fact that hospital beef-tea contains so much uric acid is interesting, and a pint of this beef-tea, I am informed, was made by cooking 1 lb. of meat for eight hours.

It appears, then, that this process extracts about five times as much as I have obtained from similar muscular tissue, but then I only boiled it for half an hour. (See chapter xviii.) This seems to render it probable that I have only extracted from the tissues in the above table from a-quarter to half of the uric acid they really contain; getting relatively more from the younger or softer tissues which broke up more easily, and relatively less from the older and tougher tissues.

Then I find that a single supper or dinner of soup, fish and meat (see fig. 16) appears to increase the urate excretion of the following three or four days by about 4 to 6 grs.; but the animal food taken at such a dinner, including soup and meat extracts, probably does not exceed the equivalent of three-quarters of a pound of meat, so that the results of digestion appear to correspond fairly well with those of long cooking in the case of the above beef-tea.

And now for our second question—How much animal food is necessary for nutrition. I shall not go deep into theoretical considerations or the writings and experiments of others, but shall state in a very few words the results of my own experience.

I believe that urea may be safely reduced to about 3 grs. per pound of body weight; at this level I form (see p. 10) 1 gr. of uric acid for 12 lbs. of body weight, whereas, if my urea stood at 4 grs. per pound, I should form 1 gr. of uric acid for 9 lbs. of body weight, and also introduce much more. I think my excretion given (p. 10) of 2.6 grs. of urea per pound is rather low, but during my experimental investigation I have tried all kinds of diet, and in some periods have certainly reduced urea both

more than is necessary and more than I should advise others to reduce it.

No doubt the whole of the nitrogen required to furnish this urea may be obtained from the vegetable kingdom, but the rule I find useful in practice is simply this—to eat as much fruit, vegetables and vegetable products (other than alkaloids) as I feel inclined for, and to add as much milk, cheese and egg as is necessary to keep my urea about this level.

I used to say fish, but the figures just given seem to show that it is quite as bad as meat, and I had long been suspicious that this was so from the effects in myself, which seemed to follow any increase of its quantity; and now that I know that uric acid is directly absorbed, it is no surprise to find that fish contains about as much as meat, which accounts for its effects, so that the only animal foods which are moderately safe are milk and cheese.

With regard to eggs I have made repeated physiological experiments, and though I cannot say that they introduce no uric acid or xanthin, it does seem that the rise of uric acid which follows their ingestion is less, relative to the rise of urea than it would be if urea had been raised to a similar extent by the ingestion of meat or fish, so that I think that eggs should come next to milk and cheese, and are to be, other things equal, preferred to meat or fish.[1]

Then again, a diet which consists so largely of fruit and vegetable products will keep the blood well supplied with alkalies, and so all the uric acid which is formed will remain in solution and be excreted, and there will be no storage or accumulation in the body.

The point is to keep urea about the level named, and to get the animal nitrogen necessary for this purpose from such source as shall introduce into the body as little as possible of uric acid ready formed; but where for one reason or another milk or cheese cannot be taken or digested, animal food in some other form may be used, and, provided that bread and fruit are eaten in fair quantity and exercise is not neglected, while urea does not rise much above 3 grs. per pound, no great harm will be done, and a *modus vivendi* will be found between functional disease on the one hand

[1] The whole point of the diet treatment of uric acid disease is to cut out the butcher, and live by the baker, the dairyman, and the fruiterer, and if these things are well taken urea will be kept at three grains per pound without the addition of eggs.

and starvation on the other. It seems that to some people the term vegetarian diet suggests nothing but huge piled-up dishes of potatoes and cabbages, and they rush after these things, forgetful of the fact that they are not very nourishing, and may prove difficult of digestion, the result being that they add dyspepsia and deficient nutrition on to their other troubles.

But this is an unfortunate and quite unnecessary result of their zeal outrunning their knowledge and discretion.

Such people forget entirely that beyond their fish, meat and fowl there are many important articles of food which are supplied from the vegetable kingdom, and that because they have been asked to avoid soups and meat extracts, and to reduce their meat, fish and fowl to half or quarter of their usual quantity, taking milk and cheese in their place, they are not necessarily reduced to potatoes and cabbages.

If it is necessary to increase their vegetable food they have the whole range of bread stuffs and prepared vegetable products to choose from, and there are plenty of fruits which are both more palatable, more nourishing and more digestible than the vegetables named above.

In all these ways, then, we shall get the uric acid in the body and blood under our control, and so long as we keep up this control we shall find that we have prevented the diseases which are due to its presence in excess.

Before going further, there is one good old failacy—the offspring of imperfect observation—to which I must again devote a little attention.

Several years ago (*Brit. Med. Journal*, vol. ii., 1888, pp. 10 and 11) I pointed out that Sir A. Garrod had fallen into an error of some importance in his argument regarding the results in a table which he quotes from Lehmann.

From this table it may be seen that the uric acid urea relation on a

Mixed diet is	1	to	29.
Animal diet	1	to	38.
Vegetable diet	1	to	22.

And Sir A. Garrod draws from this the inference that uric acid is not so much influenced by the nature of the food as urea is, and further, that animal diet does not increase the formation of urate, but rather the reverse, while a vegetable diet does increase it.

But these figures refer only to short periods of time. They refer, therefore, to excretion merely, and tell us nothing whatever about formation, and introduction.

Undoubtedly, the first effect of animal diet, as of uric acid itself, is to diminish the excretion of uric acid because it raises the acidity (p. 72), and conversely a vegetable diet increases the excretion of urate because it lowers acidity; but if these investigations had been continued for weeks and months straight on, it would have been seen that the diminished excretion on animal diet would have been balanced later on by a plus excretion of more than the equivalent amount, and the plus excretion on vegetable diet would gradually have fallen towards the level of formation—1 to 33, or 1 to 35—when all previous accumulations had been removed.

As a matter of fact, formation never varied in relation to urea one jot, being the whole time at or about 1 to 33, or 1 to 35, only on animal diet part of the urate formed and introduced failed to be excreted and was kept back and retained in the body, while on the vegetable diet some little urate previously formed obtained enough solvent alkali to effect its solution and excretion.

The figures are, I doubt not, perfectly correct, and agree in every way with my own results; they refer, however, only to short periods of time, and owing to the prevailing idea of excessive formation of urate the conclusions drawn from them are, I believe, erroneous in the extreme.

Liebermeister (*Vorlesungen ueber Specielle Pathologie u. Therapie*, vol. iii., p. 42) falls into similar error, as he says (my translation) in early times it used to be thought that in gout one ought to limit the use of proteid substances as much as possible in order to put a stop to the excessive formation of uric acid. One forgot, however, in taking this simple view of the matter that it is not of much consequence how much nitrogenous material is oxidized, but only whether it is more or less completely oxidized; and he goes on to say a healthy man excretes so much urea and so much uric acid in twenty-four hours, but an increased consumption of proteids increases to a corresponding extent the urea, but not the uric acid.

That is to say, he infers that because the *excretion* of urate is not increased by a meat diet, relatively less urate is formed, or,

as he would probably put it, it is further oxidized into urea and got rid of.

The real fact is, I believe, that urate is *formed* in proportion to urea just as it is on any other diet, and animal food also introduces some urate ready formed, but excretion falls short of formation and introduction owing to rising acidity, and some part of that formed and introduced is held back in the body, and can be washed out and produced at any future time by administering a dose of salicylate, alkali, or other solvent; or, if the curves of excretion are watched sufficiently long, it may come out of itself when from some natural cause the acidity falls.

I think, therefore, that once for all we may free our minds from this bugbear of formation, oxidation, and other more or less theoretical myths, and believe that for all practical purposes uric acid is always, and on all diets, formed in the relation to urea of about 1 to 33, or 1 to 35, while certain foods also introduce a small quantity of uric acid or xanthin ready formed.

I have been much interested to observe that the results I obtained in myself by swallowing uric acid Hypoxanthin, &c., (pp. 64 and 68) have been paralleled by those of W. von Mach, as this experimenter fed fowls on Hypoxanthin and found that it increased the uric acid they excreted (Arch. f. experim. Path. u. Pharmak., bd. xxiii., s. 148).

Whether it will be excreted in that relation is a totally different question, for excretion, as I have pointed out, can be varied at pleasure in almost any direction, and within very considerable limits. And it is by taking excretion as proof of formation that the authors above quoted have fallen, I believe, into serious error. I do not assert that uric acid is never formed in excess of the relation to urea 1 to 33, or 1 to 35—my experience is too small to carry such a proposition; but I do assert, of all the diseases of which I have written, in so far as they are due to uric acid, that they are due to its accumulation in the body from large formation and introduction, and failure of excretion; that I have never met with any evidence of formation in excess of the above ratio, or any reason to think that all the urate I have met with could not have been accounted for by failure of excretion.

For my part, I return without hesitation to the doctrine of early times, and fight uric acid disease by reducing the income of

nitrogen, believing that the clinical observation of Cullen "that gout seldom attacked persons employed in constant bodily labour, or those who live much upon vegetable diet," is a more valuable guide in treatment than many more recent conclusions founded on imperfect observations. We now know that constant bodily labour facilitates excretion (p. 160), while vegetable diet diminishes both introduction and formation, as well as facilitating excretion.

I have now also the best of all proofs of the correctness of my reasoning in practically complete immunity from a disorder which formerly threatened to interfere seriously with my work.

Such a result must speak for itself even if the theory on which its explanation is founded is destined eventually to give place to a better one, the product of still wider knowledge.

For the rest, I am quite unable to see that my reduction of animal nitrogen has done me any harm. I am as well, to say the least, weigh as heavy, and am as fit for exertion of mind or body on this diet as on any other.

Professor Humphry says (*British Medical Journal*, vol. i., 1888, p. 512), that 62 per cent. of the aged take but little animal food, and I should link this with Cullen's observations, and the very deadly effects of many of the diseases mentioned in previous chapters.

In altering diet, however, it is necessary to exercise some care, especially in regard to the amount of urate that may be stored in the body. In a man of middle age or beyond it, who has lived heartily, without stinting either meat or wine, there is sure to be a large collection of urate in the body; and if his nitrogen is reduced, and his acidity runs down, this will be dissolved out and flood his blood; for weeks and months there may be a plus excretion of urate, and its results will be more evident than pleasant; he will worry you with continual complaints that he is getting weak, that he is dying, that he has headache, depression, &c., and may even talk of suicide.

But to be forewarned is to be forearmed; and in such cases you must give a course of solvents (preferably salicylates) to remove the urate accumulations *before* you complete the alteration of diet; these must be continued for several weeks, or better two or three courses of several weeks with intervals; after this choose a favourable opportunity in the cooler part of the year, autumn or winter, for reducing your nitrogen, and all will go well.

As I have said several times before (see *Practitioner*, April, 1891, p. 279), I believe that the great majority of Britons of the present day could live very healthy and hearty lives on such a diet as I recommend, if they would make a rational attempt to do so.

To get them to make the attempt, however, is generally the difficulty; they think the diet must be lowering, and believe that beef steaks and beer are necessary for their continued existence, and undoubtedly, where the change of diet is allowed to produce considerable uricacidæmia, as it will do, if the stores of urate have not been previously cleared out, the resulting mental depression, with languor and disinclination for exertion, are sufficient to give some support to their assertions.

But, as I have shown, such results are quite unnecessary; they are not due to the new diet, but to the amount of urate which has been accumulated on the old one; and if, as I suggest, the precaution is taken of first clearing out as much as possible of these accumulations, and then of making the change of diet in the cool season of the year, when the temperature does something to keep up the acidity; and, if further, the change is made gradually, and acids and other tonics are given for a little at first, the difficulties are not, in my experience, by any means insuperable.

As I have just said, the difficulty is to get people to try; they are so often frightened by the proposal that they will make only a very half-hearted attempt, which is insufficient to carry them through any little troubles that they may meet with at first, into the smooth water beyond, when all accumulations of urate have been eliminated, and formation and introduction reduced. I have never seen anyone who wished to go back after arriving at this stage.

The amount of animal nitrogen to be allowed in any given case should be determined by the effects on urea. For slight troubles, such as headache, or mental depression, when not severe, it may be sufficient to merely reduce considerably the amount of meat taken. In epilepsy, on the other hand, it may be necessary to take no animal food, but milk, and not too much of that; and further, to purge pretty actively, so as to cause wasting and loss of strength, as in the case I have mentioned (p. 141).

In Bright's disease we have not only to reduce the formation and introduction of uric acid, but we have to accommodate the deranged metabolism by giving albumen in that form, which, according to Professor Semmola, requires least elaboration to fit it to become a natural constituent of the blood, namely milk.

For practical purposes, I am in the habit of classifying foods in three divisions :

(1) *Those to be entirely avoided*, as soup (made from meat), beef-tea, meat extracts, strong tea, coffee, or cocoa, and other vegetable alkaloids or substances that are rich in them.

(2) *Those to be reduced*, meat (especially liver, kidney, lamb, and veal), fish (especially herring), fowl, game.

(3) *Those to be increased*, milk, cheese, perhaps eggs, bread stuffs, vegetable prepared products, fruit, vegetables.

It will often be found that when animal food is thus reduced, vegetables and fruits can not only be taken in much larger quantity, but can be better digested and assimilated, than was the case when they formed part of a diet containing much animal nitrogen ; and much the same remark may be made about butter, fat, and sugar, which, in my experience, can now be taken to any desired extent. It is apparently a Jewish law not to eat butter or milk for a considerable time after a meat meal. (See *British Medical Journal*, vol. i., 1892, p. 640.)

A good many people consider fruit and sugar, either mixed or separate, to be deadly poisons, and things which the gouty should altogether avoid ; and I have no doubt that, as regards an ordinary mixed diet this is perfectly true. If these things, directly or indirectly, raise and keep up the acidity by originating fermentation in the intestinal canal, they will, undoubtedly, tend to precipitate urates upon the joints, and do harm in any arthritis, which is due in part, or in whole, to urate irritation ; but if the urate be first of all removed, and is not continually introduced in excess, they will have nothing to act upon, and will do little or no harm.

To show that there is no starvation involved, I will just give a sketch of the diet which I use, and which keeps my urea about the level of 3 grs. per pound.

Breakfast.—A large soup plate, half full of porridge, eaten with milk. (I prefer it made with salt.)

A few mouthfuls of egg, prepared in various ways ; or some mushrooms, tomatoes, or other vegetable, and occasionally fish.

One to two rounds of bread, or its equivalent in toast or scones, with plenty of butter.

A cup of milk (previously boiled) flavoured with tea, coffee, or cocoa.

Finish with a small quantity of any fruit that is in season.

Lunch.—Potato and one other vegetable, cooked in various ways (a plain boiled potato, the summit of ordinary English vegetable cookery, I never have on my table; my cook has been educated to better things than that), eaten with butter, fat, or various sauces.

Pudding, tart, or stewed fruit.

Biscuit and butter, with cheese.[1]

A little fruit as at breakfast.

For drink, a little milk, which in winter, is often warm; or, water often taken, in summer, with a little fruit syrup, such as Stower's Lime Juice Cordial.

Afternoon Tea.—Bread and butter, and cake of various kinds.

A little milk and water, flavoured with tea.

Dinner.—Soup, made without meat stock. (See receipts in "Maigre Cookery," by Sidney Lear: London, Rivingtons.)

Fish, or an egg, or a small bit of meat is occasionally substituted for these.

Two vegetables, with sauces, butter, or fat.

Any ordinary pudding, tart, or stewed fruit.

Biscuit and butter, and perhaps cheese, if the quantity of fish or egg has been small.[1]

A good supply of various fruits for dessert.

For drink, water with fruit syrup, aerated waters, or a little milk, which I often take warm in winter.

A tumbler of water, aerated water, or in winter, hot water at bedtime.

It is not necessary to interfere with established habits as to wine, beer or spirits, unless they are obviously doing harm, for once the introduction and formation of urates has been reduced, the effects of these beverages in preventing elimination may almost be neglected.

There is obviously, no starvation about this diet; but I do not say that it has no difficulties. The chief of these is, that it is not

[1] Biscuit bread and bread-stuffs are taken in considerable quantity, not a mere mouthful or two, as is often the case with meat eaters; and those who attempt to reduce their meat without increasing their bread-stuffs are likely to get into difficulties.

the ordinary accepted diet of the country; and the second is, the result of this, namely, that those who do our cooking are profoundly ignorant on the subject of vegetable cookery, and in large houses, restaurants, and hotels, the chef looks after the soup, fish and meat, and some of the more elaborate sweets, but the vegetables are handed over to the third or fourth kitchen maid, and the result is too often an uninviting mash, more suited for the food of cattle and pigs than of *fin de siècle* human beings; fruit also is often unobtainable or very bad, but all this can be remedied; and with a juster appreciation of the value of vegetable food, and the folly of indulging in an excess of animal food, I have no doubt that it will be remedied.

Some may say, "Are you not a little rash in thus running amuck at the accepted diet of the country; surely the majority of the race know what is best for them?"

But, I think that a very small acquaintance with the history of the human race shows that, in highly civilised societies, a great number of habits and customs grow up, which are by no means those best suited to promote the strength and permanent endurance of the *genus homo sapiens*.

And we here in England, do we not die younger, and in greater number than there is any necessity for? Are we not afflicted with an infinite number of diseases, which cause far more pain and misery than is at all necessary? Are we not given to all kinds of debauchery and excess, and have we not huge asylums full of lunatics, and prisons full of criminals?

I look upon all these things as serious and wide-spread diseases in the human race, and as I am not one of those who believe that Nature herself, if she had a free hand, would tend to destroy us, but rather to preserve what is good and eliminate what is evil, and further, cannot believe that the tendency to these evils is part of the ground plan of Nature's work, or that the unalterable bias to have headache, epilepsy, mental depression, mania and their results—murder or suicide—alcoholism, morphinism, cocainism, &c., is originally implanted in our nerve centres, I am driven to the conclusion that not a few of these evils are the result of unnatural conditions, and that prominent among these is unnatural diet, the evil action of which we are now in a position to follow out more completely, through our knowledge of the powerful effects of urates on the function and nutrition of the whole body.

Such a provisional conclusion is justified by my own experience and results. I was originally told that my tendency to headache, high arterial tension, and other evils, was inherited—in fact, a part of my structure and function, which, though it might be modified and relieved by drugs, could not be eradicated; and no one ever suggested a radical change of diet.

By great good fortune, and more or less by chance, I found out that a change of diet was the one thing needful, and what is, practically, complete cure has resulted. I have now only one subject for regret, namely, that I did not find this out earlier in life, as I cannot undo the evils and injuries that were accomplished while the warnings of functional disturbance remained unheeded, through ignorance of their causation.

To a very large extent, therefore, I disbelieve in inherited weakness, innate delicacy, or transmitted neurosis, in so far as such expressions apply to the diseases mentioned in the preceding chapters. The only factor about my headache that I inherited was probably a slight variation in the size and distribution of the arteries at the base of the brain, rendering my intracranial circulation specially liable to be affected by unduly high blood pressure;[1] the other factors in its causation were improper food, impure blood, and consequent increased blood pressure, but the improper food being done away with, the "neurosis" became a matter of history, in spite of the anatomical factor which remains as before.

I believe that much the same argument may apply to nearly every disease mentioned in this book, and that while certain anatomical or physiological peculiarities may undoubtedly dispose certain individuals to suffer sooner than others, or in one way rather than in another, nevertheless the food factor is common to all of them, and its adequate consideration and treatment will always result in prevention or cure. The first step towards this object is the full and complete recognition of the fact that for all practical purposes they are diet diseases, and that gout and rheumatism, for instance, may depend quite as much on the inheritance of the dollars necessary to obtain meat and wine as of any anatomical or physiological peculiarities.

I am very pleased also to be able to add that quite a large number of fellow-sufferers have now had similar experience—not that the diet is successful in every case. I have never met with

[1] *Brain*, Spring and Summer Number, 1893, p. 250.

any treatment which could honestly lay claim to so large a proportion of cures. Some are unable to alter their diet, being unable to eat at all when a change is attempted; others apparently alter their diet and yet are not cured, but these cases are the exception, and require further investigation before anything definite can be said; possibly fish has been taken too freely in place of meat. On the other hand a considerable number of sufferers in the profession have applied my suggestions to their own cases, and report that they have every reason to be pleased with the result. One of these concludes a letter recently received, by saying: "Beyond doubt I have established the fact that much, if not all, of my ill-health and moral disturbances were caused by eating butcher meat, the metabolic products of which I was unable to eliminate."

I will now say a few words as to the most useful drugs for clearing the blood of uric acid. Of the very numerous drugs which have this effect, I prefer the iodides, mercury in some form, or the iodide of mercury, or, if it is necessary to act quickly, the nitrites, or a subcutaneous injection of morphine.

The iodides seem to be specially useful where the effect has to be kept up over a long period, as in relieving the high tension of chronic Bright's disease. Mercury is useful in headache or mental depression, and iodides in asthma.

All these drugs, however, have the drawback that their action is followed by a rebound as soon as they are withdrawn; the uric acid which they clear out of the blood is not cleared out of the body, and as soon as the drug is withdrawn the blood soon takes up the uric acid which has been accumulating during its action.

The best way out of this difficulty appears to be to alternate these drugs with a course of salicylate of soda, which eliminates the uric acid and prevents the accumulations from becoming very large.

And salicylates are themselves useful in lowering pulse tension and clearing the blood of uric acid: but their greatest effect in this direction takes a day or two to come out, for, during the first two days of their action, while the excretion of uric acid is very large, the urine is scanty and the arterioles are not so much relaxed as they would be by drugs of the mercury and iodide class, which clear the blood of uric acid within an hour or two at most.

Salicylates are useful also in headache to follow the mercury

that has been used at first and remove the uric acid it has retained, and in the same way they may be useful in mental depression; and they may, as I have said, completely prevent fatigue, and will relieve it and its myalgic pains when present.

Salicylates also are very useful in some cases of asthma and in what are known as feverish colds. They will often relieve dyspepsia, especially if there is pain, and in what I have called gout of the intestines their effect is sometimes wonderful.

Similarly in anæmia they are of use, and apparently pass the uric acid through the blood without allowing it to do any harm, and the same in paroxysmal hæmoglobinuria and Raynaud's disease, though in the attacks drugs belonging to the mercury and iodide class may be used in the first place.

In albuminuria and Bright's disease salicylates when they increase the excretion of uric acid often make the urine scanty and the albumin appears to be increased; but I have never been able to satisfy myself by actual estimations that there was in these cases an absolute increase of albumen. Still, in these diseases I generally prefer drugs of the iodide class, and only use salicylates occasionally to clear out accumulated urates.

Of the use of salicylates in rheumatism, glycosuria and diabetes, I need hardly say any more, and in gout I believe that they have only to be given in proper cases and in sufficient doses to have their powers fully appreciated. I am glad to see that professor Tyson, of Pennsylvania, considers them by far the best remedies in this disease. (*Therapeutic Gazette*, November 15, 1893.)

It is not my purpose to go minutely into the drug treatment of each condition, for, in so far as any of these diseases are due to uric acid, the only real treatment is that by diet, which is both preventive and curative, while drugs for the most part (except the salicylates) relieve only for a time, and the trouble will return as soon as they are left off, and in not a few cases will be worse than if they had never been used.

If any of the troubles in the first fourteen chapters are associated with a slow high tension pulse and scanty urine, the presumption is in favour of an excess of uric acid in the blood, and this and the urine may be examined: but if this is impossible drugs may be given which would have the effect of clearing the blood of uric acid and their effects observed; or, on the other hand, caffeine or uric acid in some other form may be given to see

if it eventually makes matters worse. When the diagnosis has thus been fortified, treatment by drugs and diet may be proceeded with.

Dyspepsia may complicate any or all of these conditions, and when it is severe may to some extent prevent drugs from raising the acidity and clearing the blood of uric acid.

It will not, however, interfere with the drugs which are independent of acidity, such as mercury and other metals, whose uric acid compounds are insoluble, unless it prevents their absorption from the stomach and intestines, and in this case mercury can be administered in other ways.

In all cases, however, it is necessary to reckon with dyspepsia, and if possible to cure it; it is partly a cause and partly an effect of the excess of uric acid in the blood, and it fortunately happens that many of the drugs and the diet which is useful for uricacidæmia will also relieve or cure the dyspepsia; for instance, my so-called bilious attacks, and the dyspepsia which preceded and accompanied them, have disappeared along with my headaches.

Dyspepsia also must be kept in mind both in gout and rheumatism, and in chronic rheumatism it is often an important factor; it very probably keeps up more or less constant excess of uric acid in the blood, and then, owing to formation of acids, exposure to cold or other cause, a rise of acidity retains some of it from time to time in the joints and increases their irritation.

The treatment of uræmia is, I think, the treatment of high arterial tension, together with more or less œdema of the membranes and excess of cerebro-spinal fluid, which have been caused by the high tension; the treatment of the high tension may be the same here as in other conditions; but it may be necessary to do something more to remove the œdema, and it seems probable that venesection would be the most likely thing to succeed, for it would not only complete the reduction of tension, but would probably cause the blood to take up available fluid from all directions, and we know that morphine and venesection have been found useful in this and kindred conditions. Uræmia also has occasionally been observed to terminate in an attack of gout, which of course would mean the practical clearing of uric acid out of the blood and relief of high tension. (See paper by Dr. Ralfe in *Transactions of the Medical Society of London*, vol. xvi., p. 216, and *Lancet*, vol. i., 1893, p. 415, also case in *Lancet*, vol. ii., 1889, p. 1118.)

I have mentioned in several places (pp. 23, 75, 120 and 129), some points in the pathology of gravel and stone, and I shall now merely remark that whatever the influence of other factors, an excessive excretion of uric acid is not very rarely the most important point in their causation.

Thus they are met with in old people who have suffered for years from gout and other signs of excess of uric acid in their body and blood, and are a natural result of failing metabolism in such people. Thus I have explained that those who have much urate in their joints may, as appetite and digestion fail and their acidity runs down, excrete for weeks and months an excess of uric acid till the joints which at one time were full of urates, show nothing but empty erosions of cartilage.

As the excess of uric acid from this source passes through the blood it contracts the arterioles and diminishes the flow of water from the kidneys, so that we get a large excretion of urates and very little water to carry it off, and it is little wonder that some of this urate is occasionally deposited in the kidney or the passages below it.

Now this is a very painful and troublesome condition, and one with which it is very difficult to deal satisfactorily ; for it may be difficult to stop the plus excretion of urates, for the patient is often so feeble and his acidity so low that acids are overpowered ; but mercury and iodides will act, and these will not only diminish the excretion of urates, but will, at the same time, increase the excretion of water. Soda and potash may be given, but they will not increase the water, and will increase probably the actual excretion of uric acid.

The urates are probably doing no harm in the joints, and nothing will be lost by letting them stay there a little longer, or come out into the blood and urine more gradually, so that I am inclined to think that the iodides form the best line of treatment to adopt. I am here speaking merely of the greater or less excretion of urates from gouty joints and other places of deposit in the body, and not of the treatment of a calculus in the kidney or bladder already formed ; the line of treatment I suggest is intended to prevent their formation if possible.

It is an obvious conclusion from my reasoning that if a patient such as we find thus suffering from gravel in old age had altered his diet, in the way I am suggesting, twenty or thirty

years before, he would in all probability never have suffered either from gout or from gravel.

The effects of exercise on nutrition, metabolism, and the excretion of urea and uric acid I have already spoken of (p. 160), and from the fact that it stimulates and increases metabolism, and improves the circulation through almost all the organs and tissues, it is easy to understand that regular exercise, short of fatigue, should be extremely useful in many of the disease processes of which I have been speaking. Thus in high tension and headache it relaxes the arterioles and relieves the intra-cranial pressure; in mental depression Professor Lange has specially pointed out its value; then want of regular exercise is one of the most common causes of dyspepsia, with all its train of bodily and mental ills. Again, in albuminuria and glycosuria so much regular exercise as will keep up the nutrition of the skin, the muscles and the important glands, is often one of the chief points in treatment. In gout also, as we have seen, regular exercise will prevent attacks.

In many cases, then, I consider such regular exercise as second only in importance to diet, and the two can often be employed together with advantage. Where the surroundings or condition of the patient prevent satisfactory exercise, massage, which is in many respects equivalent to exercise, may take its place; and especially where nutrition is low it is often an important help at the commencement of treatment. Then, again, massage is extremely useful, as has been so ably demonstrated by Dr. A. Symons Eccles,[1] in improving the circulation and nutrition in joints and other structures which have been damaged by urates, or have had their nutrition seriously affected by the circulatory changes which these substances produce, thus completing the cure of which the removal of the urates is only the first step, for obviously the removal of urates, while perhaps preventing further structural or nutritional change, will not restore the tissues to their original healthy condition.

[1] *British Medical Journal*, vol. ii., 1888; *Ibid.*, vol. i., 1891, p. 1,075; "Sciatica" Macmillan & Co., 1893; *Lancet*, vol. ii., 1893, p 924

CHAPTER XVIII.

Instruments and Methods.

It is not my intention to devote space to a general consideration of instruments and methods; I shall merely state shortly those I have used, with a few remarks as to what I think about them.

Acidity of the urine can be estimated with a graduated solution of soda of which 1 cc. = 6.3 milligrammes of crystallised oxalic acid, and a solution of phenol-phthalein, which gives a pink colour in alkaline solutions.

Process.—10 cc. of urine are placed in a small china saucer, and a drop or two of the phenol-phthalein solution added. The soda solution is then run in from a graduated pipette till a slight pink tinge is permanent. The amount of soda solution used is then read off, and multiplied by the number of 10 cc. in twenty-four hours' urine, and this worked out gives the total acidity of the twenty-four hours in grammes or grains of oxalic acid, and this is the way it is recorded in my curves.

Urea.—For this I have used the apparatus of Dupré, which can be obtained from Messrs. Griffin & Sons, Garrick Street, W.C. Its essential point is that the inner tube which collects the gas has two openings at its upper end, one communicating by a rubber tube with the reaction bottle, and another ending in a short rubber tube which can be clamped just before using, when all the levels have been adjusted.

The chemicals required are a saturated solution of caustic soda, and some bromine, which can be obtained in glass tubes containing the exact amount used (2.2 cc.).

Process.—Measure 22.8 cc. of the soda solution, and place it in the reaction bottle. Drop in a bromine tube so that it breaks on coming in contact with the bottom of the bottle;

remove the broken glass and mix the chemicals by shaking round and round. The result is a pale yellow solution which is now ready for use, though if it is at all warm it should first be allowed to cool.

Measure 5 cc. of urine and place in a small tube about two inches long, supplied with the reaction bottle; place it gently with a pair of forceps inside that bottle; adjust the cork in the bottle, and lower the inner collecting tube till the water stands at the line marked 0; lastly, clamp the upper tube of the collecting tube. Now take up the reaction bottle, and incline it to one side so that the urine in the little tube and the hypobromite solution mix, and continue to move the bottle from side to side for a minute or two till they are thoroughly mixed and the resulting effervescence is over. Place the reaction bottle on the table, and allow five minutes or so for it to cool, then raise the inner tube so that the water stands at the same level both outside and in, and read off the amount of gas on the graduations of the inner tube, which is so arranged that it gives, not the quantity of gas, but the percentage of urea which has been calculated from it. Say that the percentage on the tube is 1.5; this must be corrected for temperature and pressure, and the method of doing this can be found in any general work on physics.

It is important to see that the bung or cork and the tubes fit well, and continue in good order; this can easily be tested by raising the inner tube and clamping its openings when it is full of air; it can then be lowered into the water, and if the fluid rises into it, gradually replacing the air, there is a leak, which must be found and repaired.

Uric Acid.—The process originally described by Professor Haycraft in the *British Medical Journal*, vol. ii., 1885, p. 1100.

Apparatus.—A water or mercury suction pump to be obtained from Griffin or other instrument makers.

A flask fitted with a rubber bung perforated in two places. A small funnel is fitted into one of these perforations, and an elbow tube into the other.

The elbow tube communicates, by means of a rubber tube, with the suction pump, and the funnel is half filled with broken glass, the surface of which is shaken level, and then a pulp of asbestos, shaken up with water, is poured on to it, and the water allowed to run through while the suction pump is worked, till a

uniform felt of asbestos ¼ inch thick has collected on top of the broken glass; this is further washed by passing distilled water through it till the washings are clear of fibre, and then the filter with suction pump attached are ready for use.

The other things required are several glass flasks of 100-200 cc. capacity, a 10 cc. and a 50 cc. measure glass, and several pipettes graduated to ½ cc.

The following chemicals are necessary :—

Bicarbonate of soda.
Strong ammonia sp. gr. .880.
Ammoniated silver nitrate solution.
Special dilute nitric acid.
Ferric alum, a saturated solution.
Centinormal ammonic thiocyanate solution.
Strong solution of common salt (Na. Cl.)
Bottle of distilled water.

NOTE.—These chemicals, with directions for carrying out the process, can be obtained from Messrs. Savory & Moore, 143, New Bond Street, W.

All being ready a sample of 25 cc. of the 24 hours' urine should be measured out and placed in a glass flask.

Before doing this I always note the colour, clearness, specific gravity, and the acidity (as above) from the whole bulk. If there is a turbidity or a deposit of urates, and if, as is generally the case in these circumstances there is a high sp. gr., *i.e.*, above 1020, I generally add to the whole bulk an equal volume of warm water, which, as a rule, clears it completely.

If in addition there is a deposit of red pepper crystals at the bottom of the collecting glass (and it is well to have a 3000 cc. glass jar graduated to 50 cc. and fitted with a bung for collecting the 24 hours' urine), I generally warm the whole bulk of the urine, adding some bits of solid caustic potash (the acidity having been previously estimated), and shaking till it is clear that all the uric acid has passed into solution.

A 25 cc. sample is then taken, and it must be cooled by placing the flask in cold water before proceeding.

To this add bicarbonate of soda (Haycraft says 15 grains, Hermann says 30), and I am in the habit of adding about 30 grains or a trifle more, then 2 or 3 cc. of the strong ammonia, and about 2 cc. of the ammoniated silver nitrate solution. This last brings down a gelatinous precipitate of urate of silver, and if

there is much of it the fluid is quite thick, and rapidly comes to rest after shaking round the flask.

If the patient is taking an iodide it will be necessary to add far more of the silver solution than the 2 cc. mentioned, but I will return to this point again.

We have now a precipitate of urate of silver, together with silver not combined with uric acid in an alkaline solution; the next process is to separate the silver combined with uric acid from that not combined with it.

The liquid containing the precipitate is now thrown on the filter, and the suction pump put in action; the gelatinous urate of silver remains on the filter, the fluid passes through, and the urate on the filter is washed with distilled water till the fluid passing through contains no trace of silver.

The best way to ascertain this is to take two test tubes, and in one of them place 1-2 cc. of salt solution, and then pour into both test tubes some of the liquid passing through the filter. So long as the liquid in the tube with salt solution is distinctly more turbid than that in the tube without salt solution, more washing is required.

When the urate precipitate is thus got quite clear of uncombined silver, the special nitric acid solution is poured over it, filling the filter up to the top, and keeping it full for a minute or two by pouring a little more on as it runs down.

As soon as all the nitric acid with the urate of silver in solution has run through, fill the filter up with distilled water, and let that also run through, and we are now ready for the final stage of the process.

Take the flask containing the urate of silver dissolved in nitric acid and water, detach it from the suction pump by removing the rubber bung.

Add to the solution two or three drops of the ferric alum solution (indicator) and run in from a graduated pipette, the ammonic thiocyanate solution till a permanent pink colour is produced. Read off the amount of thiocyanate used in cc., say it is 18 cc.: then 18 × .00168 gives the amount of uric acid in 25 cc. of urine. *i.e.*, .03024 gramme, and this multiplied by 4 gives grammes in 100 cc. = .12096, and this multiplied by the amount of urine passed, gives the total uric acid for the 24 hours in grammes.

When the urine contains iodides, the silver combines first with the iodide, and second with the uric acid; in other words, till enough silver has been added to combine with all the iodide present, urate of silver is not formed, so that if only the ordinary quantity of the ammoniated silver nitrate solution is added, the amount of uric acid may be greatly under estimated.

The best way out of this difficulty is to add at once 4 to 6 cc. of the silver solution, then to filter and add to the filtrate more silver solution and see if any more iodide of silver comes down, if it does filter again, and again add more silver; when iodide ceases to form on the addition of the silver solution, add 2 cc. of that solution and filter finally; you will now get all the uric acid combined with silver and retained on the filter, and you can then proceed as before.

By this process, which I owe to the kind suggestions of Mr. J. E. Saul, F.I.C., I have been able to obtain the same amount of uric acid from a urine, both before and after the addition of an iodide.

Haycraft's process takes from 30 to 40 minutes to complete; longer for high sp. gr. urines, shorter for dilute, for much urate of silver clogs the filter and greatly increases the time required for the washing process; so that time is saved by diluting high sp. gr. urines; but when a urine of sp. gr. 1025 is diluted to 1 in 4, there is probably some increased loss of urate in the washing process, as the gelatinous urate clogs the filter and aids its own filtration, which, up to a certain point is more perfect, the more there is of it.

Those who have a centrifugal machine driven by power can separate the urate of silver by this process instead of by the filter; it takes, however, at least three-quarters of an hour to do: but once set going, only requires attention once in every fifteen minutes, and several specimens of urine can be worked at once, according to the size of the machine. I am indebted to my friend Mr. W. H. Symons for this information, and have tried the method myself: but having no water power to drive the machine, it is not so convenient for me as the filter and suction pump.

I think that Haycraft's process thus described, while taking quite a moderate amount of time, gives very accurate and constant results; when there is any doubt I repeat my observation, and

very rarely find a difference of more than ½ cc. of thiocyanate solution between the two; if there is a greater difference than this, I go in for further investigation, and may find that a fragment of glass has perforated the asbestos and put the filter wrong, and when this has been put right, I again repeat my observation.

Though the process takes thirty to forty minutes to complete, a large part of that time it requires only an occasional look to add water when it runs through, and other matters can be attended to, and then if the suction pump is powerful several filters can be connected with it and several urines worked through at the same time.

It is, I think, a distinct advantage of this process that it can be worked on 25 cc., or even 12½ cc., of a high specific gravity urine, for when the urine of a single hour or less, which you may want to estimate in a case of headache, fits or paroxysmal hæmoglobinuria, amounts only to some 20 or 30 cc., processes which require 50 or 100 cc. of urine cannot be used, and it would by other processes often be quite impossible to estimate the uric acid in small quantities of blood, muscle, or other organs which can be done by this process.

To estimate the uric acid in organs and tissues I have used a process given by Salkowski and Luebe ("Die Lehre von Harn," p. 94) for blood.

It consists simply of throwing the blood or tissue finely divided (I pass solid tissues through a mincing machine) bit by bit into ten times its volume of boiling water. The coagulated albumen is removed by filtration or decantation and the fluid evaporated down to about the bulk of the original blood or tissue. I then apply Haycraft's process just as for urine.

As I found that long boiling of tissues appeared to increase somewhat the amount of uric acid obtained from them, I adopted the uniform plan of boiling for half an hour after all the tissue is in the boiling water.

It is by this process that I obtained the results given in chapters iii. and xvii. When tissues contain uric acid visible under the microscope or to the naked eye this process yields a very large quantity, and the final evaporation need not be carried so far.

Supposing, however, that such great accuracy is not required,

and that for clinical purposes all one wants to know is that a patient is passing about half as much uric acid again to-day as he was yesterday, or that the urine which was excreted at the time of a fit or headache or an attack of paroxysmal hæmoglobinuria contains two or three times as much as that passed in the previous hour when these troubles were absent; this knowledge can be arrived at in a very few minutes and without much trouble.

I have been pointing out now for several years that the urinary water is both from hour to hour and day to day inversely as the uric acid excreted along with it; by measuring the water from hour to hour, we can estimate the uric acid greater or less excreted along with it.

If the water in any hour is twice as much as in the previous hour the uric acid will probably be only one half of what it was, or *vice versâ* provided there is some water in the body to be excreted, and provided there has been no hæmorrhage, vomiting or diarrhœa to remove all the available water from the body.

Taken over a long period of time my lowest excretion of water is about 700 to 800 cc. in twenty-four hours or about 30 cc. an hour, and with this the excretion of uric acid in relation to urea varies from about 1—18 up to 1—25.

On the other hand, my largest excretion of water is about 2000 cc. or about 80 cc. an hour, and this corresponds to a relative excretion of uric acid of about 1—35 to 1—45.

In single hours the excretion may fall below 30 cc., or rise a good deal above 80 cc., but the urine is most scanty in those hours of the day in which the excretion of uric acid is greatest, and most profuse in those in which it is least.

If at any time when the urine is scanty there is a doubt whether this is due to uricacidæmia and retention of water (*i.e.*, if there are no other signs of uricacidæmia being present), the blood should be examined, and if the scanty urine is due to uricacidæmia and retention of water it will be found to be dilute (*i.e.*, both hæmoglobin and red cells will be relatively diminished), but if the scanty urine is due to want of water in the body, it having been removed by the skin or bowels, &c., then the blood will be concentrated (*i.e.*, both hæmoglobin and red cells will be relatively increased). In this case no inference can be drawn from the urinary water as to the presence or absence of uricacidæmia.

But bearing these things in mind, if at any time, as often occurs in the uric acid headache, epilepsy, or hysteria, the urine is 30 to 40 cc. in one hour, and 100 cc. or above in the next hour, no fluid having meanwhile been swallowed, if the urea is estimated in both hours, one will probably not be very far out if one puts uric acid as 1 to 20 of urea in the first hour and as 1 to 40 in the second, and precisely the same if the water fluctuation occurs in days instead of hours.

For many clinical purposes, and when the uric acid excretion is not required in grains for publication, this is all that one wants to know, and I am in the habit of thus reasoning from the water to the uric acid in scores of cases which I should have no time to estimate; making an estimation here and there to support my inference, if there seems to be any reason to doubt it.

Blood. Decimal.—I have estimated the cells and hæmoglobin with the hæmocytometer and hæmoglobinometer of Dr. Gowers, and the decimal spoken of by Dr. A. E. Garrod and others as "worth," is obtained by dividing the percentage of hæmoglobin by the percentage of red cells, thus $\frac{\%\ \text{Hæmoglobin}}{\%\ \text{Red cells}}$ if both are at the supposed normal (100), the result is a whole number, and not a decimal, but as this is only very rarely the case a decimal is generally obtained which represents the hæmoglobin value of each red cell. This is low as .3 in chlorosis, and .7 to .8 or above in more normal conditions.

From this decimal with daily observations a curve can be constructed comparable with the curves of uric acid and urea excretions. (See figs. 29 and 30). And with similar daily observations, it will be found that when there has been a diuresis, both the cells and hæmoglobin are increased as regards the given quantity, while when fluid is being retained in the body (dropsy), they are both diminished as regards the given quantity, and the daily excretion of uric acid can be roughly estimated from these facts alone.

But the greater or less quantity of water in the blood does not directly affect the value of the blood decimal, though when excess of water is due to excess of uric acid (uricacidæmia), the blood decimal will be found to fall.

Water in Expired Air.—I have estimated this by means of U tubes filled with calcium chloride; each arm of the tube is about eight inches long, and has a diameter of a little less than one inch.

It is closed at each end by a rubber bung perforated by a glass tube bearing a bit of rubber tubing and a glass mouth-piece on one end; the rubber tubes are closed by spring clamps. The whole is carefully weighed before use and again afterwards, and the difference recorded equals the moisture in the expired air. It is used as follows:—

Remove the clamp from the rubber tube at the far end of the U tube, and place the glass mouth-piece on the near end between the lips. When respiration is quite regular, and sitting quietly and comfortably, and the second hand of a watch is at a given place, begin to expire through the tube between the lips, inspiring through the nose; the clamp on the near tube is to be opened at each expiration and closed at its end. After a little practice, it is possible to continue to respire quite regularly, and to open and shut the tube at the right moment in each act. This is continued for five minutes by the second hand of a watch on the table, the clamp is then shut and the distal tube also clamped, and the tube is ready to be weighed.

I may say that Messrs. Savory and Moore kindly did the weighing for me, as I have no instruments sufficiently accurate.

I measured the urine passed in fifteen minutes, including the five minutes of expiratory estimation, and divided the result by three to compare with the expired water in five minutes.

The result shows that when the urinary water is scanty owing to uricacidæmia, the expired water is also scanty, and this affords the best proof that uric acid affects the arterioles in the lungs as well as those in the kidneys and elsewhere throughout the body.

Pulse Tension.—Apart from the signs to be obtained by an educated finger on the radial artery, and an educated ear at the apex and base of the heart, the sphygmograph furnishes the best clinical record of arterial tension, and has this further advantage, that the trace can be kept indefinitely for comparison with all future traces.

By pulse tension one practically means blood pressure, or such blood pressure as results from contraction or blocking of arterioles and capillaries on the one hand, and the pumping power of the heart on the other.

There is no doubt that the sphygmograph is but an indifferent gauge of blood pressure, but it tells us what is clinically of far more value—the effects which contraction of the arterioles and

capillaries produce on the heart and large vessels behind them; thus, in two cases lying side by side, the actual blood pressure may be identical; but in one case, say, with a well nourished and hypertrophied left ventricle, it may be produced by a slight contraction of arterioles, while it produces almost no effect, except a little slowing of the heart's action; in the other case, with an ill-nourished heart, the pressure may be produced by very great contraction of arterioles and capillaries, while the heart is acting irregularly, palpitating and fluttering, in a word, failing and dilating, before the peripheral resistance: all this the sphygmograph will tell us with considerable accuracy; while to be told that the blood pressure is the same in these two cases, is information of almost no clinical value.

I have used the sphygmograph of Dudgeon, and recently I have had one fitted with a pen, the invention of my friend, Mr. W. H. Symons, which I believe to be a great improvement on the old point scratching on smoked paper.

The pen consists of a little cone of metal, open at both ends and threaded with a bit of cotton. The small end of the cone with the cotton below it rests on the paper and is moved over it in exactly the same way that the old point was moved.

The only thing to attend to is that the paper must be highly glazed and very smooth, to reduce friction, and then the pen runs over it perfectly, making curves which are identical with those obtained by the old process. The instrument thus modified, with directions for use, can be obtained from Messrs. Maw, Son and Thompson, London.

The pen works best with a solution of aniline, a little of which is placed on the upper end of the little cone and is conducted down by the cotton.

In this way there is no limit to the number of traces that can be taken, as paper after paper can be passed through the machine, so as to catch irregularities of the pulse which only occur now and again, or a continuous trace can be made on a paper several feet long. The trace is permanent from the moment it is made, and there is no black to rub off, and no fixing required, so that this useful invention renders the process both more cleanly and more expeditious, and is a great help to clinical recording.

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