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 Alexander Haig.

T. Wilson Smith MD.
Bath.
May 1893.

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

ALEXANDER HAIG, M.A., M.D.Oxon., F.R.C.P.

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

WITH TWENTY-THREE ILLUSTRATIONS.

London:
J. & A. CHURCHILL,
11, NEW BURLINGTON STREET.
—
1892.

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.

CONTENTS.

ERRATA.

Page 122, line 15, for puerperal *read* peripheral.

„ 148, „ 14, for Bruce Jones *read* Bence Jones.

ERRATA.

Page	8,	line	22,	for	Raymond	*read*	Reymond.
,,	80,	,,	13,	,,	,,	,,	,,
,,	84,	,,	4,	,,	,,	,,	,,
,,	99,	,,	10,	,,	inversely	,,	directly.
,,	103,	,,	17,	,,	,,	,,	,,
,,	111,	,,	10,	,,	Raymond	,,	Reymond.
,,	129,	,,	13,	,,	veilleight	,,	vielleicht.
,,	158,	,,	19,	,,	well	,,	will.
,,	176,	,,	15,	,,	and	,,	of.
,,	184,	,,	26,	,,	inversely	,,	directly.
,,	245,	,,	14,	,,	calcicum	,,	calcium.

LIST OF FIGURES.

URIC ACID

AS A

FACTOR IN THE CAUSATION OF DISEASE.

CHAPTER I.

History.

It is now fully nine 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 very 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 reasoning 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 Raymond and others that led me to look for a uric acid reaction in epilepsy similar to that I had found in migraine.

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 might 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 six years, but taking only the totals of the longer periods of my estimation of my own excretion, we get a total of 616 days in which 6,363 grs. of uric acid, 194,617 grs. of urea, and 29,193 grs. of acid (reckoned as oxalic acid) were excreted; giving a relation of uric acid to urea of about 1—30.5, and a

relation of acid to urea of 1—6.6. In the earlier part of my researches I did not estimate the acidity, and I have therefore omitted the figures of this period from the above totals; the relations of uric acid to urea in this period varied from 1—35 to 1—38, and would have tended to bring the relation nearer to 1—33, the one made use of in my curves.

At the beginning of my work my diet was more nitrogenous, the acidity was higher, and I excreted less uric acid; on a more vegetarian diet I excreted relatively more uric acid, but as we shall see presently, this does not prove that I formed more.

Among 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 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.

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 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, obviously 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. 15.).

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 nitro-

genous 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.

And there is one other point requiring explanation. Taking the figures previously given I excreted 6,363 grs. of uric acid in the relation to urea of 1—30.5, but if I had excreted it in the relation 1—33 (the level of formation) I should only have excreted 5, 897 grs.—a difference of 466grs. It may be asked whether I think the whole of this 466 grs. of uric acid was washed out of my body by the lowered acidity of a vegetarian diet, and was not due to any extra formation of uric acid.

I reply that probably my standard of formation, 1—33, is only relatively accurate, and that this may account for part of the difference; but I should be quite prepared to believe that 200 or 300 grs. of uric acid had been washed out from the stores in my body in the time covered by these figures, and if I am correct, and if the vegetarian diet is continued, there will at last come a time when all the stores of uric acid in the body will be exhausted, and its excretion, observed over many consecutive months, will be found to have sunk to the absolute level of formation, whatever that may be.

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, 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, 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 con-

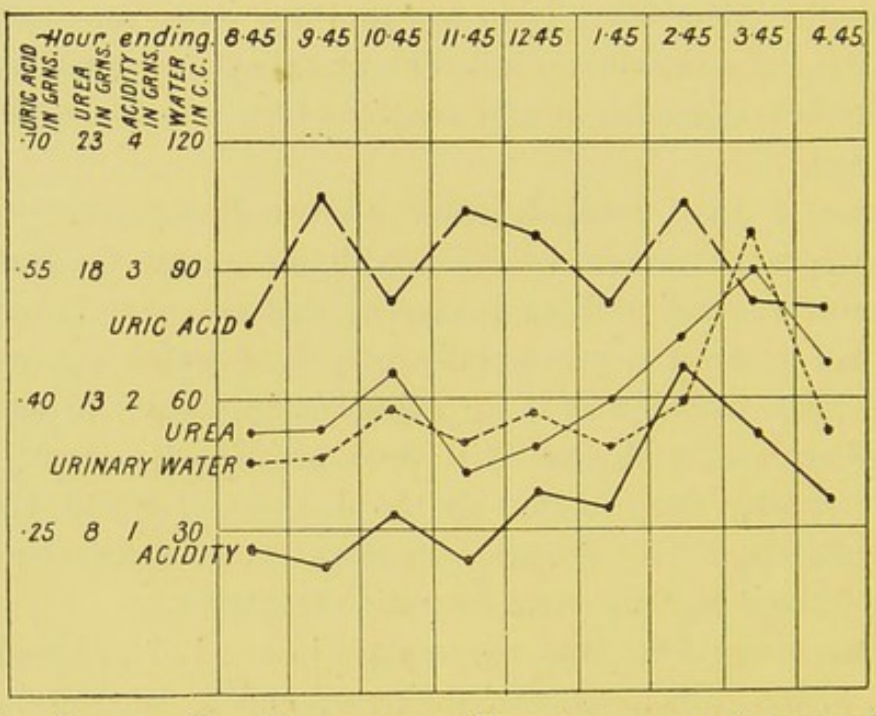

FIG. 1.—NATURAL PLUS EXCRETION OF URIC ACID IN THE ALKALINE TIDE. Breakfast ended 9.50 A.M. Lunch ended 2.10 P.M. Two and a-half miles sharp walking 3.0 to 3.45 P.M.; perspiration, and low tension pulse after walk. Total urinary water 527 cubic centimètres. Total urea 118 grains. Total uric acid 5.0 grains. Relation of uric acid to urea 1 to 23.6.

versely, 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.

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.

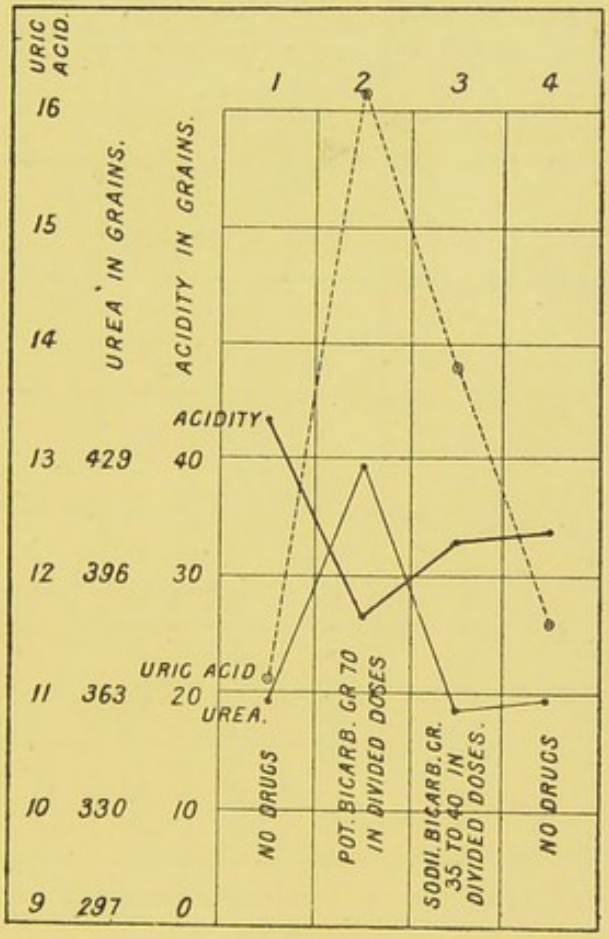

FIG. 2.—PLUS EXCRETION OF URIC ACID PRODUCED BY ALKALI.

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 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. Robert's "Work on the Urinary

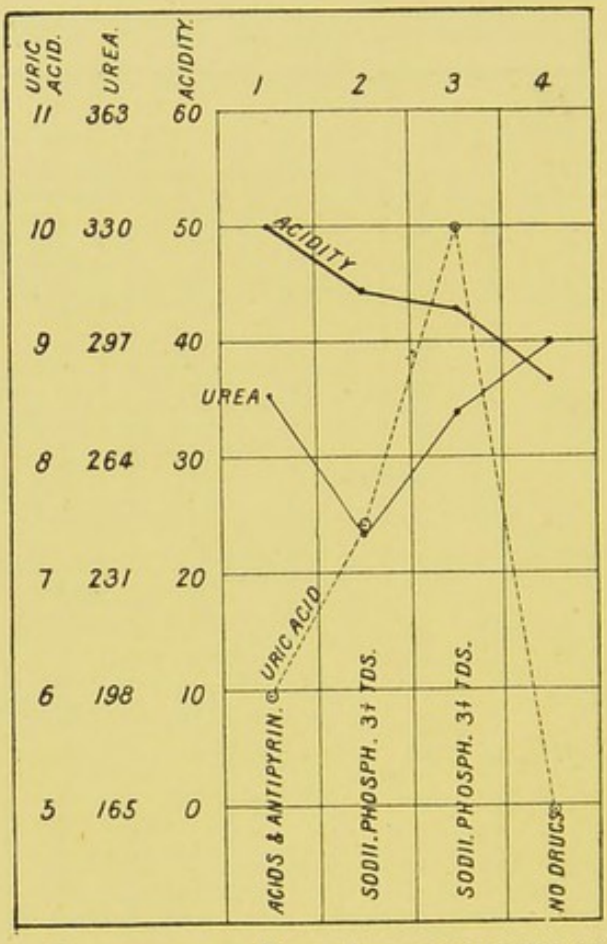

FIG. 3.—PLUS EXCRETION OF URIC ACID PRODUCED BY PHOSPHATE OF SODA.

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.)

As to salicylic acid and its compounds, I have shown that they increase the excretion of uric acid, and I have pointed out that

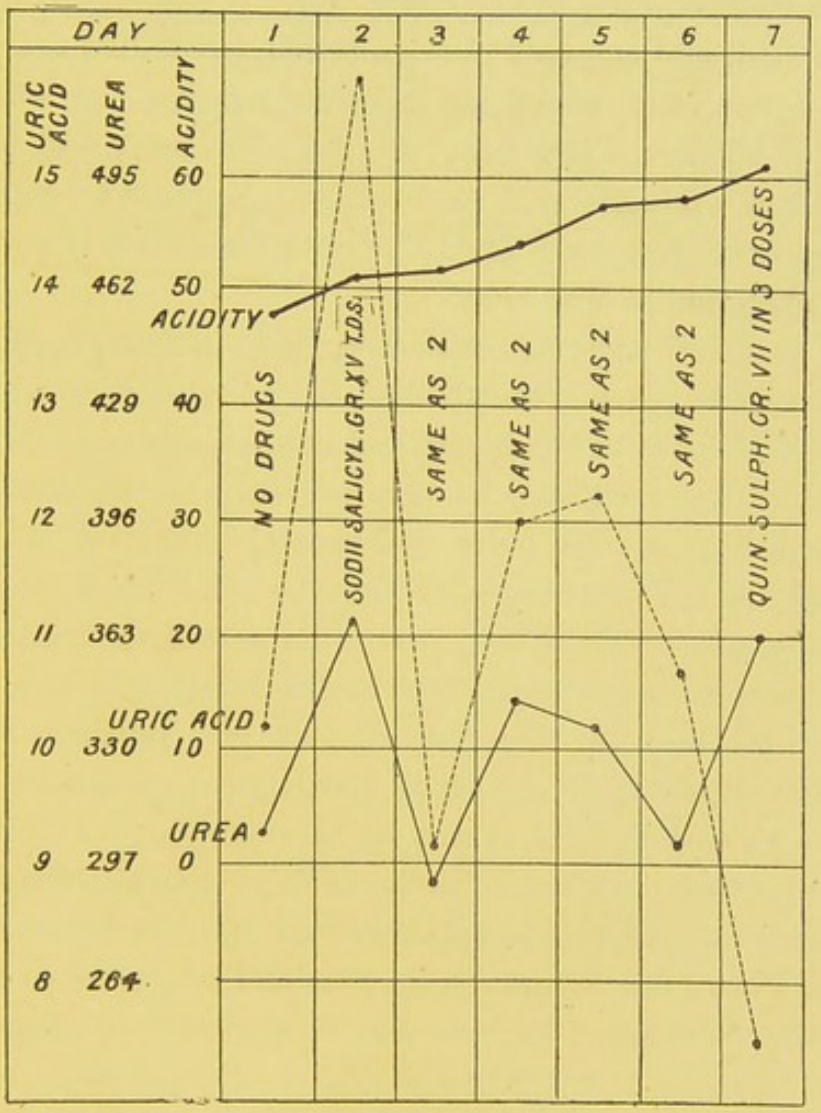

FIG. 4.—PLUS EXCRETION OF URIC ACID PRODUCED BY SALICYLATE OF SODA.

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.

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.

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 and its action on uric acid has interested me more

than most of the drugs about which I have already written, but it would require a whole chapter to go into the action of quinine, and I must confine myself here to a few statements.

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.

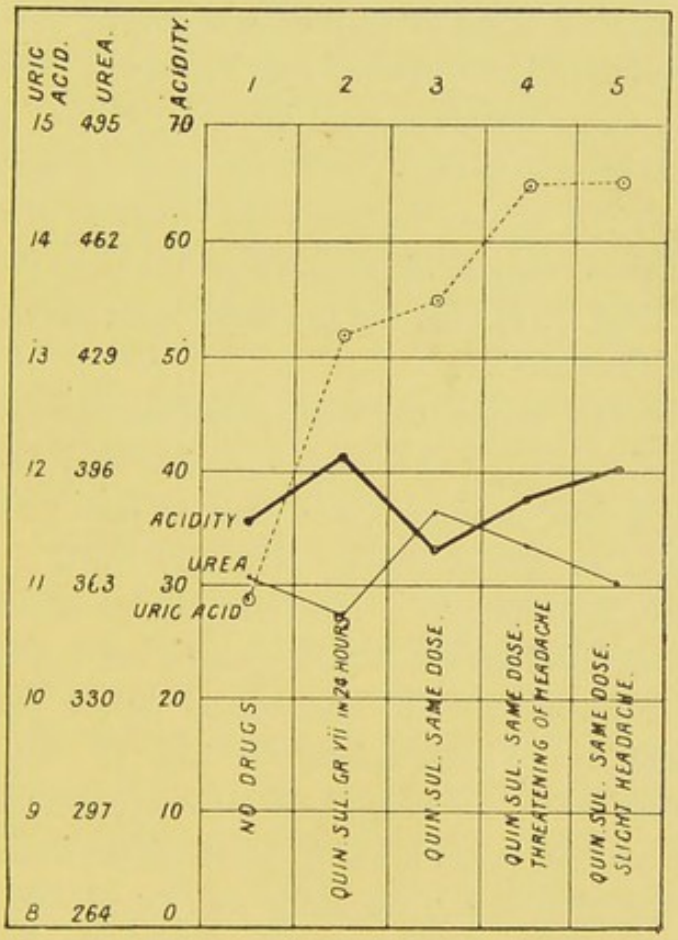

FIG. 5.—PLUS EXCRETION OF URATE PRODUCED BY SMALL DOSES OF SULPHATE OF QUININE.

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 uric acidæmia, 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 XI.

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 uric acidæmia 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 uric acidæmia 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 otherwise form insoluble compounds with uric acid, as opium, cocaine, mercury, antipyrin, caffein, 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).

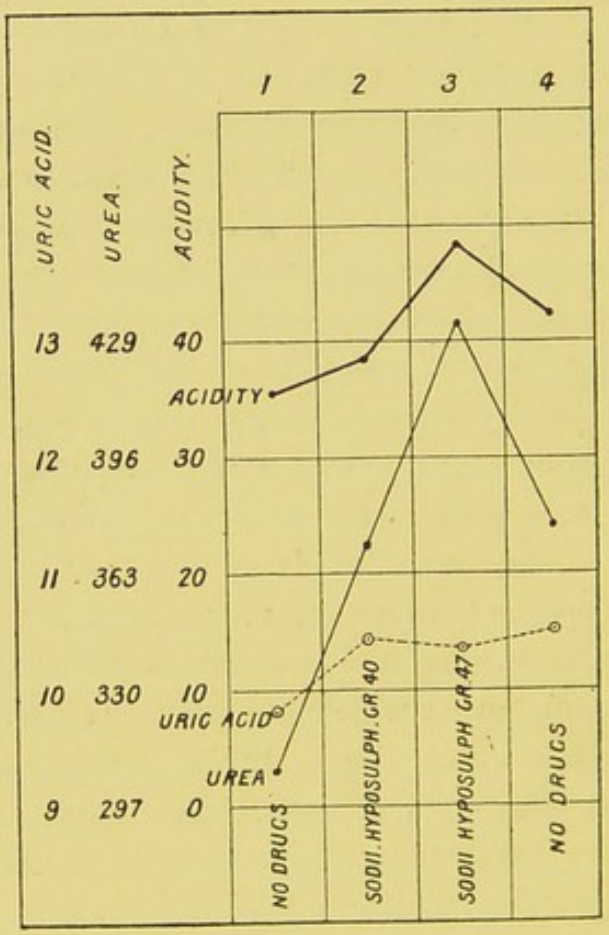

FIG. 6.—RETENTION OF URIC ACID PRODUCED BY A RISE OF ACIDITY.

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 6.6 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. 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 (*Lecons 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.

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 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.

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

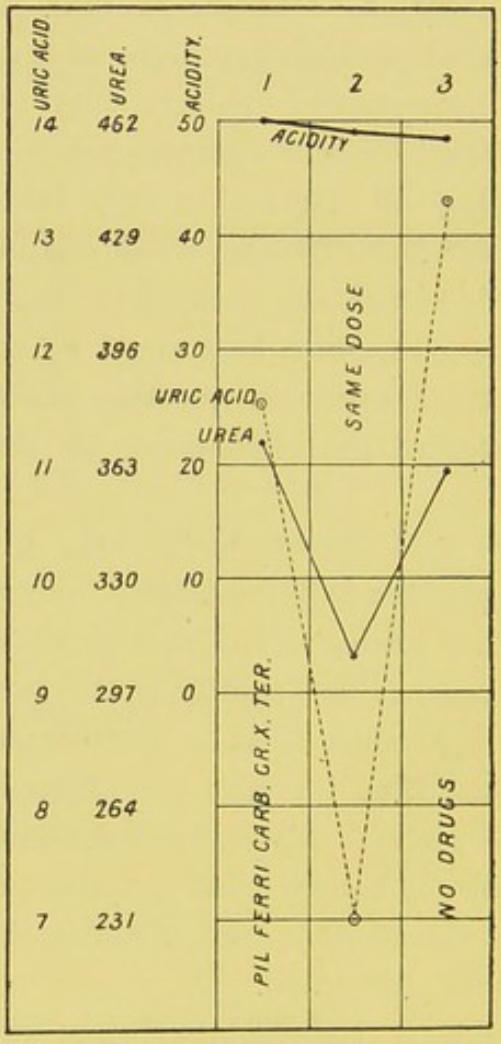

FIG. 7.—RETENTION OF URIC ACID PRODUCED BY IRON.
From *Med. Chi. Trans.*

all the available uric acid has been previously removed, none of these conditions will 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

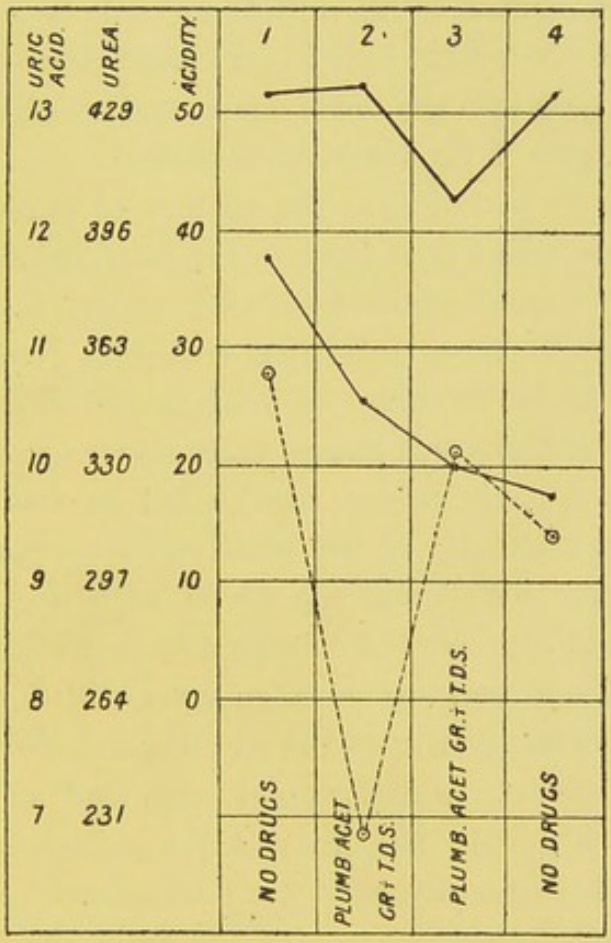

FIG. 8.—RETENTION OF URIC ACID PRODUCED BY LEAD.
From *Med. Chi. Trans.*

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 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.

---

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

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 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.

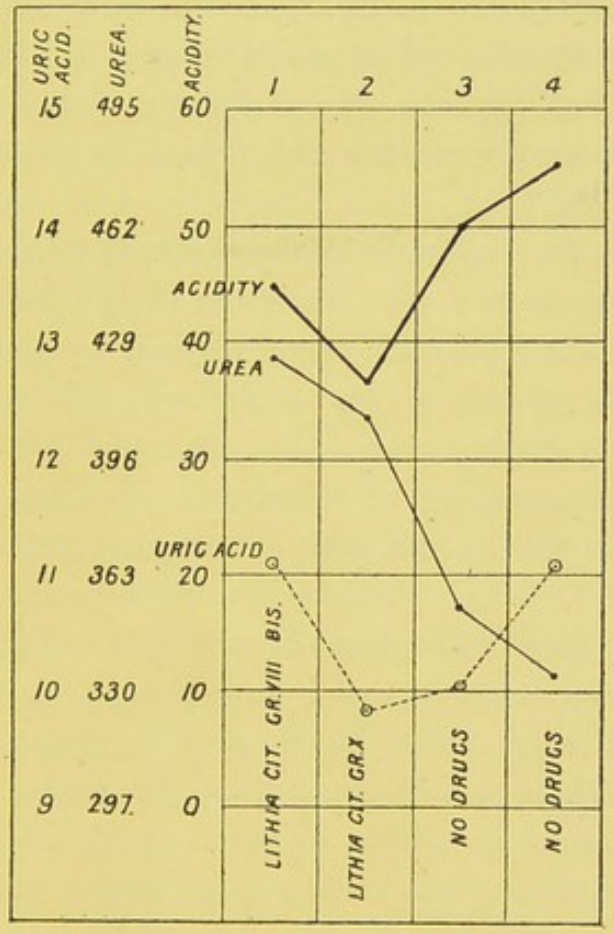

FIG. 9.—RETENTION OF URIC ACID PRODUCED BY LITHIA.
From *Med. Chi. Trans.*

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])

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

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 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 (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).

---

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

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 it diminishes the excretion of uric acid and stores it in the

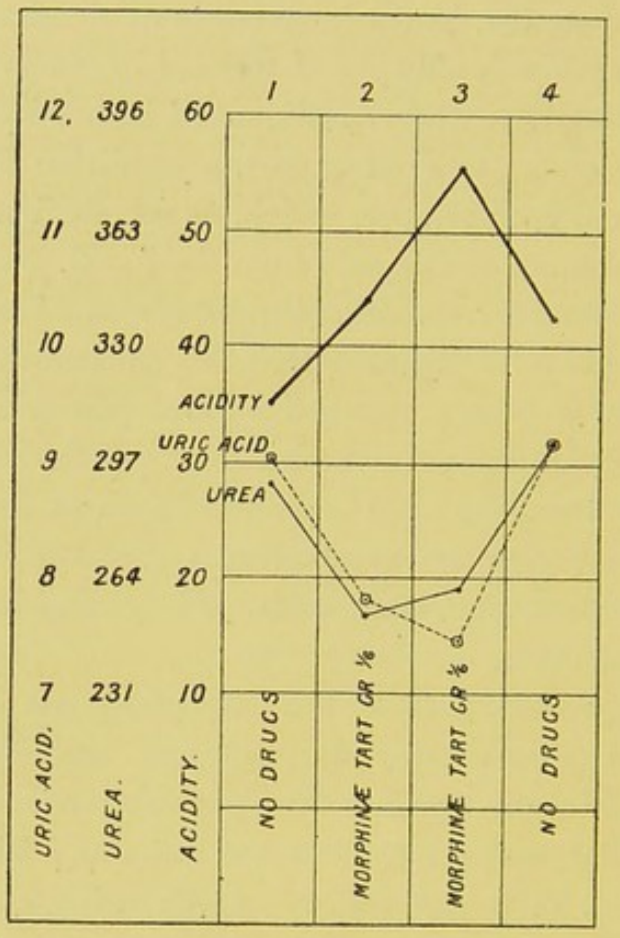

FIG. 10.—RISE OF ACIDITY AND RETENTION OF URATE PRODUCED BY MORPHINE.

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.

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 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. 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, and I hope before long to have an opportunity of using it in a case under my own care.

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 recently 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 diminish 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 leads 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. 1, 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 VI.).

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-

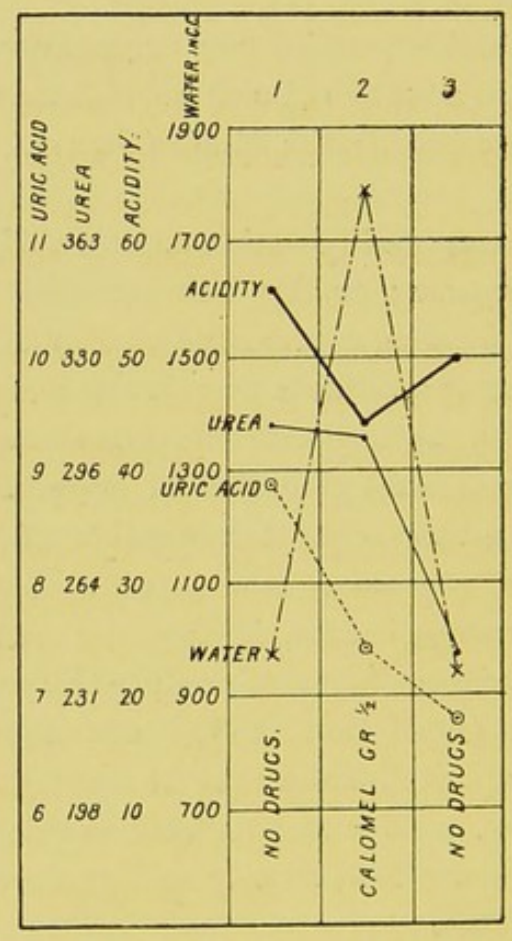

FIG. 11.—RETENTION OF URIC ACID AND DIURESIS PRODUCED BY MERCURY.

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.

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 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 precipitate 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.

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 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

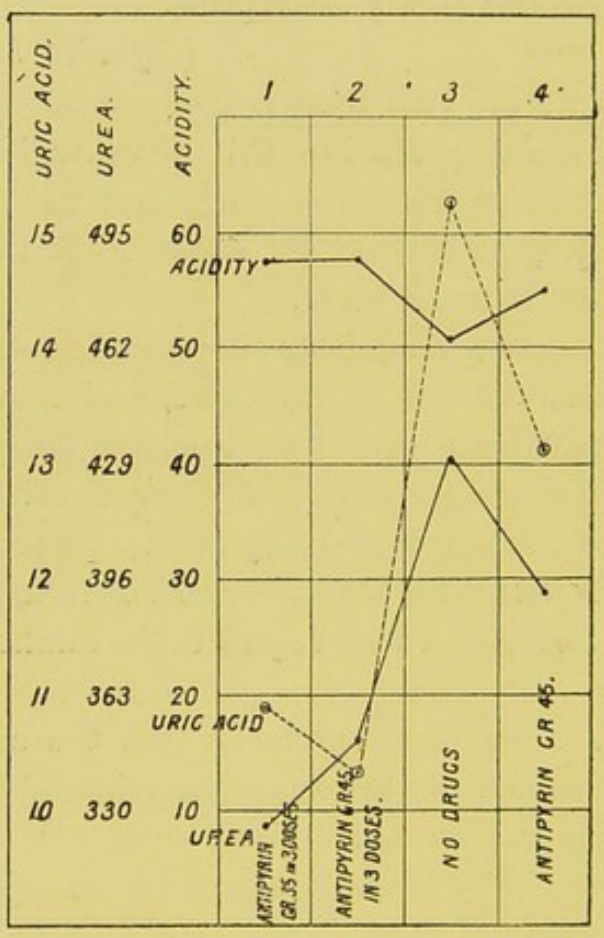

FIG. 12.—ANTIPYRIN EFFECTS ON ACIDITY AND URIC ACID.

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.

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 promot-

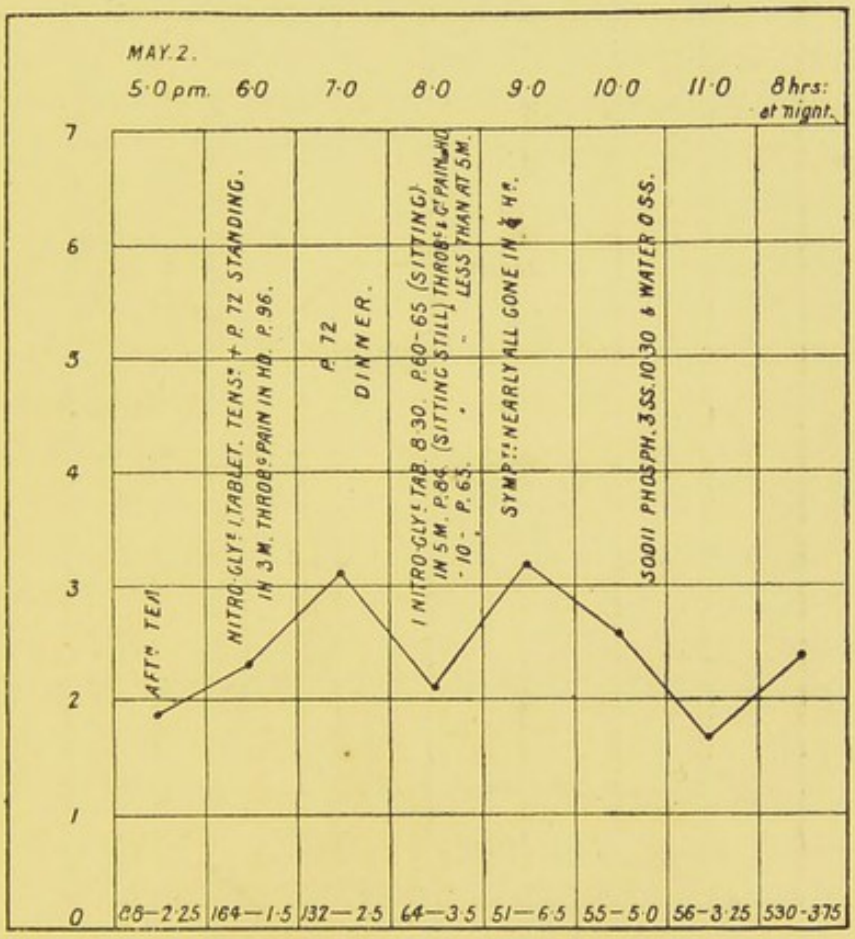

FIG. 13a.—EFFECTS OF NITRO-GLYCERINE ON THE ACIDITY OF THE URINE.

ing 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.

Caffein acts much in the same way as strychnine, and the relief of headache and diuresis which it sometimes produces

are probably due to its clearing the blood of uric acid, as in case of the similar effects of mercury, opium, &c.

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

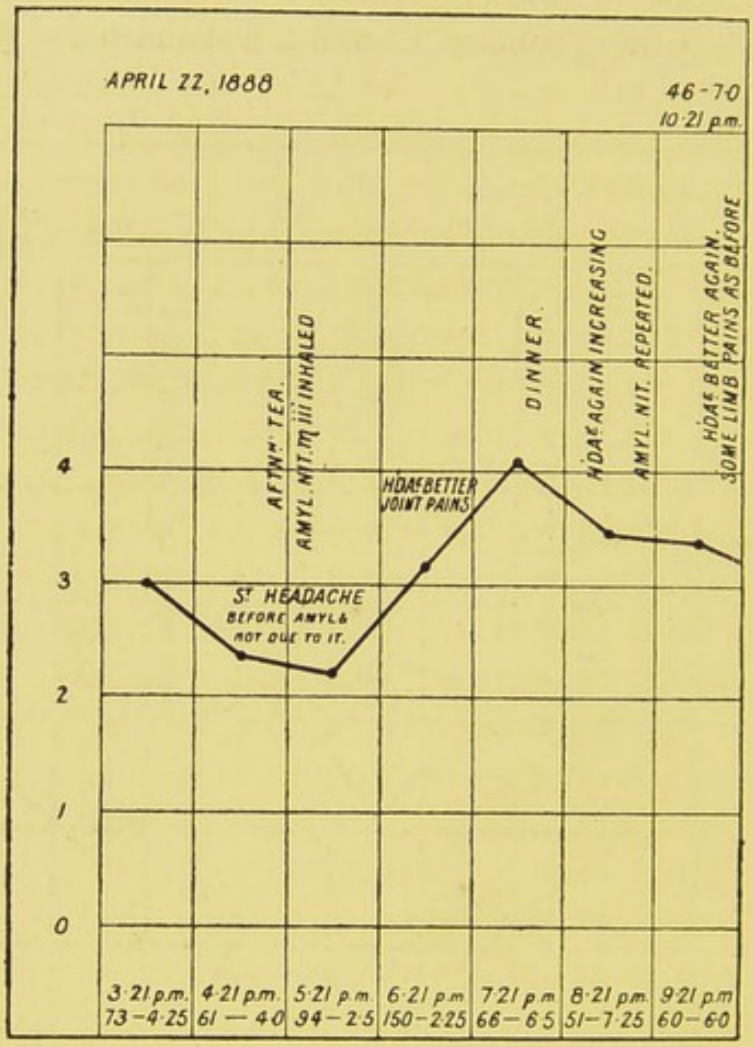

FIG. 13β.—EFFECTS OF NITRITE OF AMYL ON THE ACIDITY OF THE URINE.

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 *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 nitro-glycerine 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 don't 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 uric acid in the blood and tissues, 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

---

[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.

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 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 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 it had passed down the ureter as soon as formed there would

never have been any trouble, and to bring about the complete excretion of all that is formed 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 grs. 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) 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 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.

To guard against any misunderstanding I will just say that I do not deny that some conversion of uric acid into urea does take place in the body, and in at least two of my papers,[1] I have pointed out some of the conditions under which I believe this may occur.

Sir A. Garrod has also pointed out[2] 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[3] 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

[1] See *Journal of Physiology*, vol. viii., p. 216; and *Brit. Med. Jour.*, 1890, vol. 12, p. 124.

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

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

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 practically 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.[1]

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 one to twelve or one to fourteen. 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.

Then there is Sir A. Garrod's explanation of the presence of uric acid in the spleen, which I have so often quoted,[2] and which serves so admirably to explain many of my results.

In his Lumleian Lectures,[3] 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

[1] See Salkowski und Leube, *Die Lehre vom Harn*, p. 88.
[2] See *Journal of Physiology*, vol viii., p. 214.
[3] *Brit. Med. Jour.*, 1. 83, p. 549.

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,[1] and then having evaporated and cleared my solution, I applied Haycraft's process to it, just as in the case of urine.

Haycraft's process for the estimation of uric acid is now so well known, and is to be found in so many text books of physiological chemistry, that I need not describe it.

It has been attacked from various points, but not, so far as I know, with much success; and while some who have used it only a small number of times have ventured to criticise it, and assert that it is liable to great variation, I have contented myself with pointing out that, in my experience, extending over six years, during which I have estimated many hundreds of grains of uric acid in addition to the figures (given above)

[1] *Die Lehre vom Harn*, p. 94.

representing my own excretion, the results have been far too constant to allow of my believing in any serious variations. And recently (*B. M. J.* vol. ii., 1891, p. 10, and *Zeitsch. für Physiol. Chemie*, May, 1891.) Haycraft himself has replied to certain chemical and theoretical criticisms.

My results, however, are to a large extent independent of method ; as they agree *inter se* and are constant, and are also in harmony, as we shall see presently, with many physiological and pathological facts about which there is no dispute; many of my results can also be demonstrated by what I regard as less perfect processes than that of Haycraft, and some of them have been demonstrated by others.

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 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, all of which I have spoken of elsewhere,[1] and 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

[1] *Practitioner*, Nov., 1888; Wood's *Monographs*, New York, Feb., 1890; and paper read at Birmingham meeting, July, 1890.

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 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

[1] *Zuelzer. Semiologie des Harns*, p. 89; and *Brain*, vol., ix., p. 364.
[2] *Med. Chir. Trans.*, vol. lxxii.

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 beaf-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 pound. So that it rather appeared that the meat diet in the dog, as in man, diminished the excretion of uric acid.

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 5 and 6 grs. to the pound, 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 pounds) 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. 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 pound, 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 it, is 1 to 6.6; 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.

With regard to the effects of urates on the blood pressure and arterial tension in animals, I have several times been on the point of endeavouring to obtain a license to test several matters in this connection, and perhaps I may do so yet: but while think-

ing over it, it seemed to me that the results of influencing uric acid in man are so definite and precise, and leave so little room for doubt as to cause and effect (as we shall see presently), that what must, of necessity, be somewhat rough experiments on animals, which again differ in so many important points from man, would not add very much to our knowledge.

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 uric acidæmie" (*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 of that substance, 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 uric acidæmia 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 pleura, 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 uric acidæmia 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 during the three or four hours after breakfast 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 if I refer again to (fig. 4, p. 19.) 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 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. 23), 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 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 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

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

pointed out,[1] 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[2] 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 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

---

[1] "Some Vascular Effects of Uric Acid," read at Birmingham, July, 1890.

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

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 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 pp. 52—54.

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.

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

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

in the acidity of the urine and a fall in the alkalinity of the blood.

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 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, 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.

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.

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 alkalinity 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 uric-acidæmia (of which the signs are well-marked) without excess of urates in the urine;

---

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

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 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 30 or 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.

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.

I had perhaps better explain that by excessive formation I mean formation of uric acid in excess of its normal relation to urea (1 to 33); the absolute formation of both can be increased or diminished at any time by increasing or diminishing nitrogenous metabolism. Thus on ordinary meat diet my urea used to be between 500 and 600 grs. a day, or about 4.5 grs. per lb. of body weight, and uric acid about .136 grs. per lb. On my present diet (see Chap. XII.) urea is rather less than 3 grs. per lb., and uric acid .090 grs. per lb., and it is because the absolute formation of uric acid is thus reduced that I escape from the troubles which are due to its excess in the blood—the formation of uric acid relatively to urea has not altered in the least.

Everything then depends on the urea; when uric acid is in the urine in excess of the above relation to urea, it is being washed out from some accumulation in the body; when it is diminished relatively to the urea, it is being kept back and accumulated; if at any time the accumulations are partly washed out by solvents, this is followed by a diminished excretion till they have reaccumulated.

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 uric-acidæmia on the function, nutrition, and structure of the tissues of the human body to any required extent; and I shall go into some of these points at greater length in the following chapters.

CHAPTER IV.

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 to 6 p.m. (see fig. 16). (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 intra-cranial 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 (uric-acidæmia) 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. 14), 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, vol. i. p. 784.)

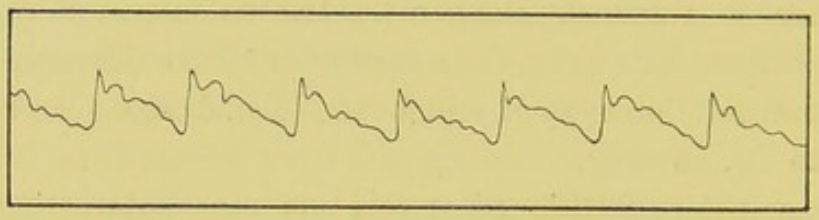

FIG. 14.—HIGH TENSION PULSE OF A URIC ACID HEADACHE. RATE 57.

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.

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 40-50 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. 15 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 gr., 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.

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.

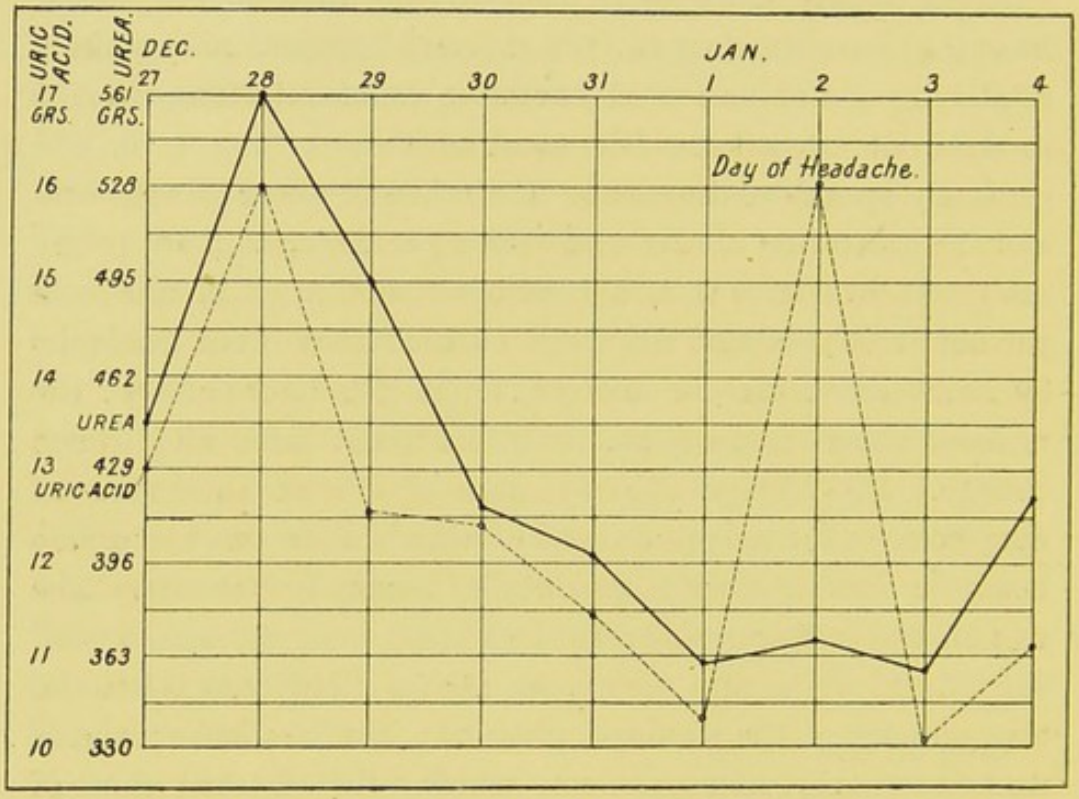

FIG. 15.—EXCRETION OF URIC ACID AND UREA BEFORE, DURING AND AFTER A HEADACHE. *From Med. Chi. Trans.*

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 300 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.

As above-mentioned the largest excretion of uric acid in the twenty-four hours takes place in the alkaline tide of the morning (a well-known fact), 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 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 to 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—6.6 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). If the urine is examined uric acid will be found constantly above its normal relation to urea—1 to 33—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 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 them being absorbed, or because, after more or less absorption 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 uric-acidæmia, 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.

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 300 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 nitrogenous 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 thus 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 Dr. 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 nephritis had supervened, and that an organic cause of uric acid retention had been added to the original functional one. (See Chap. XI.)

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 Raymond 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.

If uric acid contracts all the arterioles and capillaries of the body when it is present in excess in the blood (a matter which I shall presently go into at greater length) it requires no great power of imagination to see that under certain conditions, either in the anatomical arrangement or the physiological stability, or both, of certain vascular and vaso-motor areas, the cause (uric acid) which contracts all the arterioles and capillaries generally may produce local spasm or tetanus which, in accordance with the above theories, may account for the pain of the headache; and by such a process of reasoning we can easily understand that while uric acid probably contracts the arterioles and capillaries in everyone, it is only where there are conditions of greater sensitiveness or irritability in certain special vascular areas that it produces the conditions special to the uric acid headache.

For everyone has from time to time some uric acid in their blood, and in everyone its excretion fluctuates from day to day and hour to hour, in accordance with general laws, and while everyone gives occasionally some signs of excess of uric acid in their circulation, only those who have specially sensitive vaso motor areas in the region presided over by the cervical sympathetic suffer from vascular spasm or tetanus, and the headache it has been supposed to produce.

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 (? neuchalalgia of Dr. Burnett, see Chap. VII.) 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, and is in favour of Dr. Brunton's above-quoted explanation of the pain.

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 them, 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 uric-acidæmia and headache on the other.

When 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 Chap. XI.), generally means chronic uric-acidæmia, 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 Chap. XI., I regard uric-acidæmia 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, such as old age.

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 uric-acidæmia. I could find no morbis cordis though she had the cardiac signs of uric-acidæmia; 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 uric-acidæmia.

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 that there will be trouble in the future if it is neglected —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 uric-acidæmia; 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 (Chap. XII.) may get less credit than is due to it.

CHAPTER V.

EPILEPSY AND CONVULSIONS.

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

Thus du Bois Raymond, whose vaso-motor explanation of migraine has just 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. 75), 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. Fere, *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, as we shall see in Chap. VII. 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 uric-acidæmia.

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.

As regards the word neurosis, it will be seen that I agree with Dr. Liveing that these disturbances are due to a neurosis, *i.e.*, a condition of minus resistance or increased irritability of certain portions of the nervous system (? vaso-motor nerves) which render certain individuals more liable to be affected in these ways by uric acid than others.

The neurosis I have suggested may be inherited as part of our structural and physiological inheritance; or it may be to a greater or less extent acquired by the reaction of the organism to its surroundings through a series of years, especially in infancy; or more suddenly through the effects of injury or acute disease.

With regard to treatment, however, I consider that this knowledge justifies me in taking a much more hopeful view; for while the neurosis can rarely be altered or removed, or the nervous system influenced except in the direction, not always desirable, of stupefying it with bromides, it may I think, often (and I hope, with increasing knowledge, more often in the future than the past) be possible, by removing the uric acid, to prevent the reaction and functional disturbances it produces.

If it be granted, then, that in some cases of epilepsy the fits are due to the reaction of an unstable vaso-motor system to the irritation of uric acid, a question naturally suggests itself as to what proportion of cases of epilepsy may be due to this cause.

To this I have no definite answer, and time is required before it can be answered; meanwhile I have no wish to go one inch beyond my facts; but it may nevertheless not be without interest to consider a few points with regard to this question, even though they will not help us to answer it completely.

Since I made my first observations I have examined several cases of epilepsy, and in all that I have been able to examine with sufficient care, though their number hardly rises to two figures, I found an identical uric acid fluctuation.

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 to 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 188cc. and showed a relative excretion of uric acid 1 to 34, and No. 2 was 97cc. 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 one or two 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 p. 3).

When I first began to work at epilepsy I had the wish and intention to confirm my first results by examining the urine in a large number of cases, but having found the great difficulty of obtaining reliable specimens I was gradually obliged to give up the idea, and to content myself with observing other points in the cases as bearing on the question of uric acid causation.

Those who have a large number of epileptics under their care, as in asylums, where the urine could be separated with ease or drawn off during and between the fits might soon furnish the results of a large number of cases, and I hope that someone will do so; and though I shall never lose an opportunity of examining the urine of a fit where there is any chance of its being properly separated, I now look upon many other signs and symptoms as more or less satisfactory evidence of uric acid causation.

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 follows 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.

I am sorry to say, however, that in the case of M. H., mentioned above, diet has not, so far, been very successful. After I gave up salicylates and other drugs—though by the way nitroglycerine and morphine or acids (drugs which clear the blood of uric acid) have often appeared to be of some use in reducing the number of the fits or bringing her round out of them—I put her on a diet in which milk and occasional fish or egg was to be the only animal food. I did not insist very much upon the quantity, so long as she was careful of the quality; the diet, however, appeared even after many months' trial to have no effect upon the fits, and so I began to inquire exactly what she did eat, and I found that she had been taking two pints of milk and one egg every day, and fish occasionally as well. Now this diet contains more milk, eggs, and fish than I myself consume, and the patient is only a girl of some 15 or 16 years of age. I, therefore, told her to take only one pint of milk a day and no egg or fish, the rest as before, and since this change she has

been better in several ways, but the time (a few months) is too short to allow of any conclusions being drawn. It may be again a natural fluctuation in the severity of the fits.

I mention the matter to show that quantity must be attended to as well as quality in diet, as patients may get too much nitrogen in the shape of milk and eggs, and thus continue to form uric acid and urea in large amount.

On the other hand, plenty of cases have been recorded in which diet has done good in epilepsy, and in so far as the fits in any case may be due to uric acid it is the only indication offered, and in such cases when a change of diet is made the urine should be examined and the urea formation reduced by as much as 150 or 200 grs. in an original excretion of 500 grs. per day, provided this can be done without loss of weight or other obvious sign of danger; we should then know more exactly what we were doing. If from all this one draws the inference that just as the uric acid headache is due to excess of uric acid in the blood and its effects on the arterioles of the brain, so its nearest relative, epilepsy is, also in many cases due to disturbance of function having a similar origin, what can we say as to the way in which it may produce the fits?

As I have previously pointed out, Dr. 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 untersuchungen über anæmia und Hyperæmia des Gehirns in ihren Beziehung zur Epilepie" (*Archiv. de Physiologie*, June, 1891, p. 609).

Now it seems to me that we have in the effects of uric acid

on the circulation—about which I shall have to say so much presently—a direct cause of just such alterations in the cerebral circulation as Dr. Broadbent here refers to, and probably it may bring about these alterations in two ways: (1) by contracting the cerebral vessels directly, as it contracts the arterioles elsewhere throughout the body, producing anæmia of the brain with probable stasis in certain portions of it; or (2) by causing a great and general rise of arterial tension it may overpower the heart, which falters and flutters, as I have often watched it doing in myself; when tension is high the pulse gets slower and slower, and finally, for a beat or two stops, and down goes the patient in a faint, with or without anæmic convulsions, and this would correspond with Dr. Moxon's observation as quoted by Dr. Broadbent. See also fig. 21.

As I shall have to point out presently, anæmia of the brain produced by uric acid is almost certainly the cause of a large amount of mental depression; and if, in addition to this, there is at any time produced great slowing of circulation, or temporary stasis in certain areas, we may have in the effects of uric acid on the vessels, or the heart, or both, all the causes which, according to Dr. Broadbent may account for convulsions. Indeed, contraction of arterioles, sometimes going on to thrombosis has been seen in the retina during attacks of migraine (uric acid headache) (see Mr. Stanford Morton, *Ophthalmic Review*, March, 1890). This was almost without doubt the work of uric acid, and the same thing occurring in the cortex of the brain would amply account for epilepsy; and so long as the stasis and anæmia stop short of thrombosis little or nothing would be found *post mortem*, even though the process had been many times repeated.

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 and the heart 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 the disease, and viewed by the side of the other vascular effects of uric acid in other chapters, none of my reasoning can, I think, be regarded as wild or improbable.

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 uric-acidæmia, 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 a side-light on the possible causation of the headache and fits of uræmia? As I have pointed out, the treatment of uric-acidæmia removes the symptoms of uræmia (*Brit. Med. Jour.*, November 30, 1889). See also Chapter X.

I have never yet seen a case of epilepsy in which diet has been given a trial at all comparable to that by means of which I have cured my migraine, or in which uric formation has been reduced to three-fifths of its original dimensions, or less; but where such a diet does fail, I should be inclined to say, Make quite sure that you have not to deal with some organic cause which has been overlooked.

CHAPTER VI.

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. 14, p. 72). 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.

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.

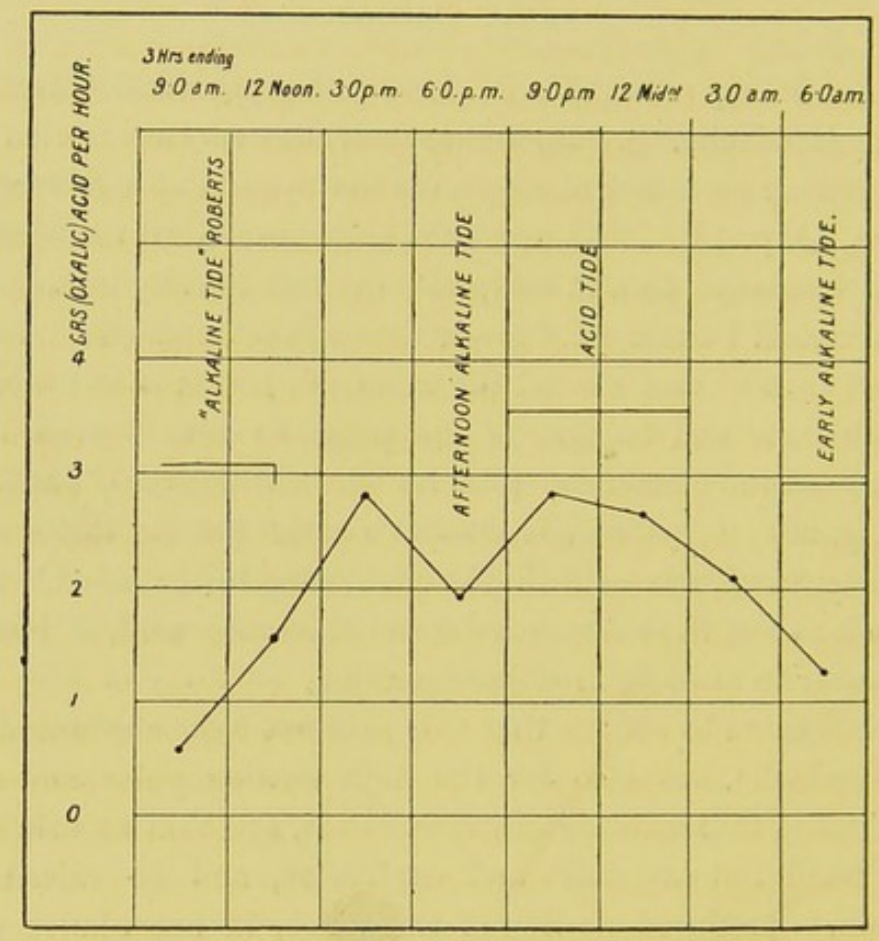

FIG. 16.—DIAGRAM OF URINARY ACIDITY FOR TWENTY-FOUR HOURS. CURVE OF EXCRETION OF ACID RECKONED AS OXALIC ACID IN GRAINS PER HOUR

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 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 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 to 33—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 the formation, 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 tissus 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. 9 to 13) 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 inversely 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.

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. xvi., p. 96) 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," p. 377):—"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. 17).

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 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.

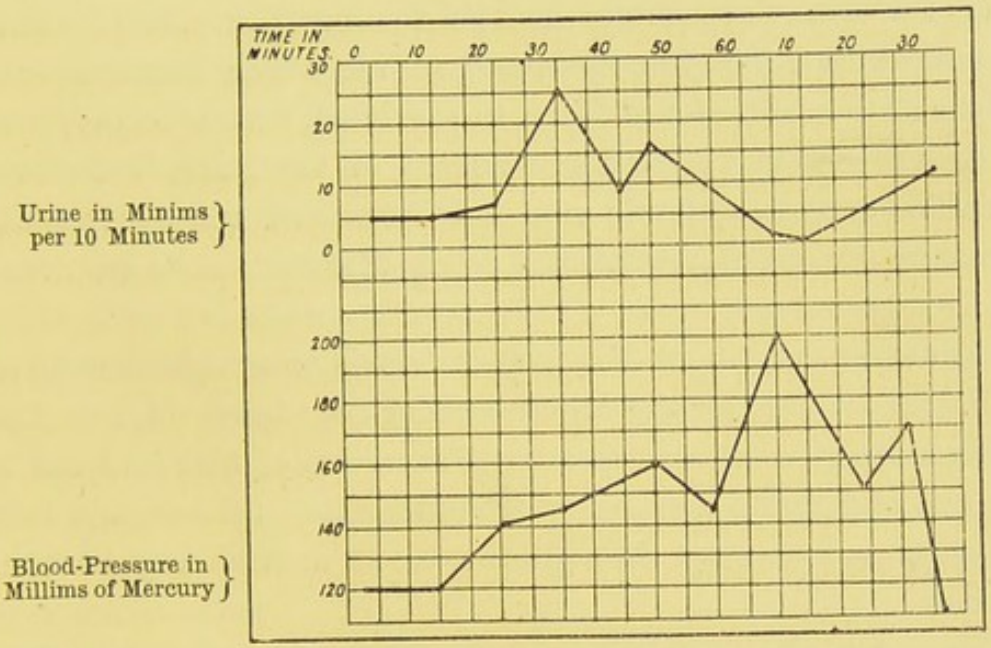

FIG. 17.—CURVES SHOWING THE EFFECT OF ERYTHROPHLÆUM UPON THE BLOOD PRESSURE AND SECRETION OF URINE. From *Phil. Trans.*, vol. clxvii.

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.

With regard to my own pulse, there is not the smallest doubt that it is at its slowest and quickest respectively within the hours mentioned, and in all cases which I have examined under physiological conditions it has appeared to me that the same rule holds.

With regard to the flow of urine I will here give a few figures. Thus I found that in a period of sixteen consecutive days the urine in seventeen hours of the day (6 a.m. to 11 p.m.) averaged 52 cc. in the hour, and in the seven hours of the night in the same period 57 cc. in the hour, that is to say, the largest excretion of water occurred in the hours with the smallest excretion of uric acid and *vice versâ*, and a glance at some more recent results will bring this out, perhaps, even more distinctly.

Thus, on the 8th of May last, 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 $4\frac{1}{2}$ 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 11th, 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 the 8th, 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 inversely 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, *B. M. J.*, 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.

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 shown in fig. xix. I have written at great length of the relaxed arterioles, quick pulse and diuresis which opium produces (see *Brit. Med. Journ.*, Nov., 1889, &c).

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. xviii. 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. xi., p. 36).

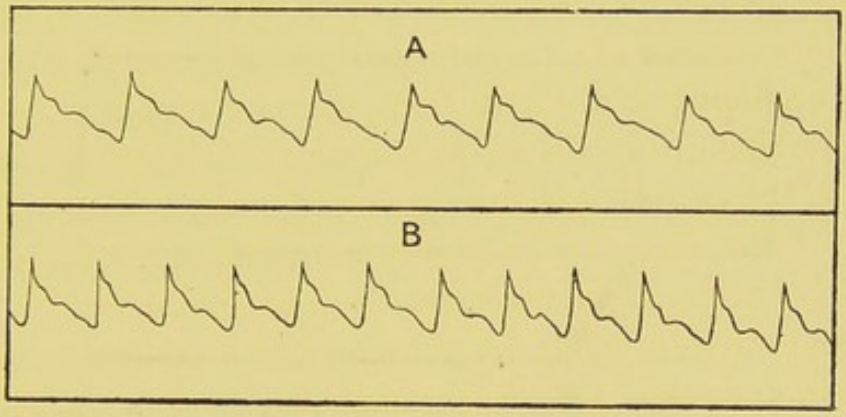

FIG. 18.—TRACES SHOWING PULSE TENSION A BEFORE AND B DURING THE ACTION OF MERCURY.

Lithia is one of the most interesting of the other drugs which produce the same results. I have given above (Ch. II., pp. 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 urine depend on the uric acid, and not on the acidity, alkalinity or other property 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.

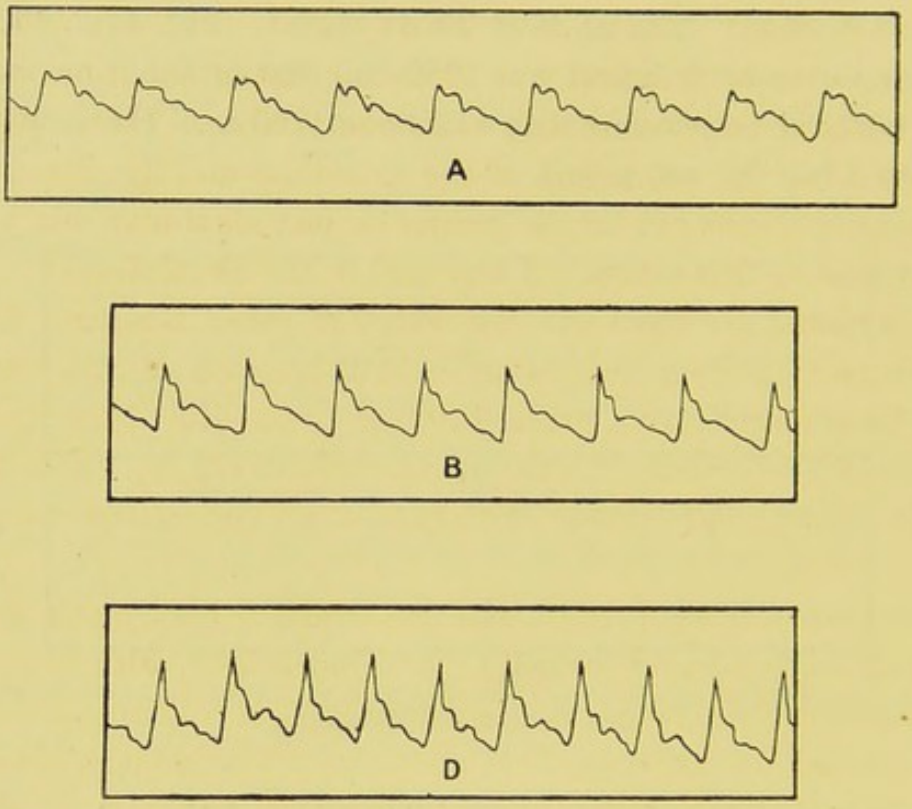

FIG. 19.—(A) HIGH TENSION PULSE OF OPIUM REBOUND. MORNING AFTER MORPHINE. 7.30 A.M. threatening of headache; pulse, 60.
(B) LOW TENSION PULSE OF OPIUM WELL BEING.
(D) LOW TENSION PULSE OF ANTIPYRIN WELL BEING.

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 to 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 to 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 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 excretion of uric acid.

Again on May 19th, 1887, with no drugs urinary water was 1670 cc., and uric acid to urea 1-32. On the 20th, with 70 grs. of bicarbonate of potash, urine was only 1260 cc. and uric acid to urea 1 to 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 excretion 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 caffein the same; the diuresis produced by caffein 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.

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 than 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 (Ch. XI.) 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 uric-acidæmia without having Bright's disease, hence nocturnal urination does not necessarily imply Bright's disease.

The excretion in my own person on May the 8th, previously mentioned, will very well illustrate what I mean. On this day there was marked uric-acidæmia in the alkaline tide, and the urine during the day was only 35 cc. per hour, but at night the acidity rose, the uric-acidæmia 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 uric-acidæmia, but this is most marked in the alkaline tide after breakfast 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 woke 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.

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 uric-acidæmia just as in the case of the temporary uric-acidæmia 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. xx.), 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.

In epilepsy the pulse is often slow and of high tension just before the fits, and I have elsewhere suggested (Ch. V.) that the contraction of the cerebral arterioles on the one hand, or failure of the heart on the other, are the actual causes 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 uric-acidæmia. The

urine excreted at the time of a fit is also scanty, and of high specific gravity.

In uræmic convulsions I have pointed out Dr. 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.

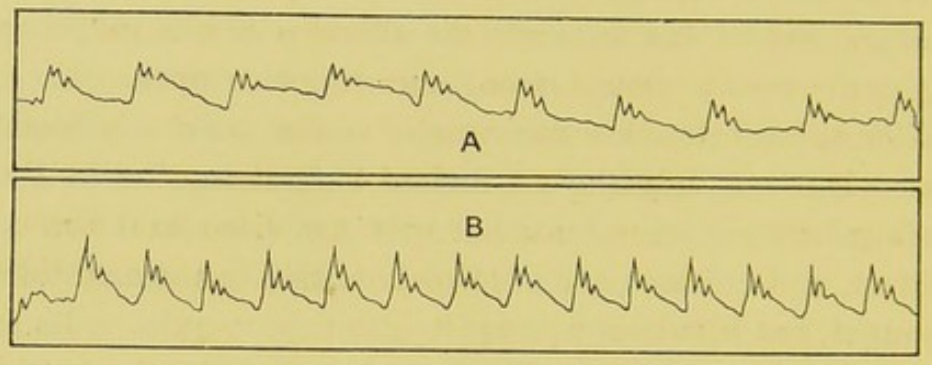

FIG. 20.—(A) PULSE 52. HIGH TENSION OF NEPHRITIS.
(B) SAME, TEN DAYS LATER, RATE 80; TENSION RELAXED BY DRUGS.

NOTE.—When the drugs were left off it returned to very nearly its original rate.

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

In mental depression and melancholia, as we shall see presently, Dr. 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 uric-acidæmia, and that they may be often relieved or cured by affecting the uric acid. 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. We have seen that in accordance with the theory of du Bois Raymond, headache is due to vascular spasm in certain areas, and epilepsy is due to a similar affection of a larger or somewhat differently placed area, and there is apparently good reason to believe that some cases of vertigo are due to just such vascular spasm affecting the region of the bulb.

It is evident, then, that all that has been said about the causation of headache and epilepsy, or that remains to be said about their 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.

From this point of view vertigo is due to vascular spasm affecting the region of the medulla or upper cervical cord, and this vascular spasm, as in headache and epilepsy, may have as one of its causes excess of uric acid in the blood (uric-acidæmia).

But there is good evidence to show that very similar results, including an extremely slow pulse, may be due to anything causing slight pressure on the bulb or cervical cord, such as pachymeningitis or local injury and compression. Probably these lesions produce the same effect on the bulb and cord that the vascular spasm does, hence similar symptoms result.

But some may say, what about the slow pulse? We have been told that arterial tension varies with the amount of uric acid that is circulating in the blood, and that the pulse rate is inversely as the tension in accordance with Marey's law, but

how does this help us to explain the slow pulse associated with slight mechanical compression of the bulb?

The obvious answer is that the urate may produce just such changes in the circulation of the bulb as are produced by the pressure of new growth or mechanical injury, hence the results will be nearly identical. The changes, however, which are due to urate will be temporary and fluctuating, while those due to mechanical causes will be more or less permanent.

In epilepsy, for instance, I have always been careful to say, while pointing out that in some cases it may be due to vascular spasm, which is due to the irritant effects of uric acid, that new growths and other local causes may produce similar vascular effects, and similar symptoms, and the position of the medulla in the causation of vertigo probably is in no way different from that of other portions of the great nerve centres in epilepsy or headache.

I have always supposed that the urate causes the contraction of the peripheral arterioles by acting on the vaso-motor nerves, and there is a great deal to be said for this action being central on the medulla itself.

To discuss this question at length would lead me into a great deal that is foreign to my present purpose, which is to point out that in the great majority of cases high arterial tension is due to excess of urate in the blood, and that when this is so the removal of the one entails the removal of the other, and that this knowledge gives us power over the tension of the pulse and the rate of the heart's action, which may be of the greatest importance.

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 uric-acidæmia of some slight functional derangement in this region, for I have several times pointed out (*Brain*, 1891, and elsewhere) that with these signs of uric-acidæmia 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 uric-acidæmia 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 uric-acidæmia, 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, Dr. Broadbent says (*Pulse*, p. 249): "There may, for example, be 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 function or nutrition, are specially affected and give rise to special symptoms.

Hence it is only those people who have these places of minor resistance or increased irritability, who suffer from headache, epilepsy, or vertigo as the effects of uric-acidæmia, while others with as much uric acid may almost entirely escape. Their

apparent immunity is, however, I fancy, somewhat dearly purchased, as they may drift without warning into the more serious troubles, such as atheroma, Bright's disease, or glycosuria, which uric acid causes, before their nerve centres give them warning that there is anything wrong.

I have previously mentioned the cold skin and extremities of the uric acid headache, and have suggested that they were due to contraction of the skin vessels by uric acid just as scanty urine is due to contraction of the kidney vessels and mental depression, as we shall see presently, to contraction of those of the brain by uric acid.

But there is what has appeared to me to be merely a further degree of the same effects of uric acid in Raynaud's disease, the first degree of which (local syncope) differs only to a very slight extent from the cold extremities of a uric acid headache. The chief point of difference is that it is local, the power of the uric acid seems to be, to a large extent, concentrated on the vessels of one region, generally symmetrically, but there is here no essential difference from the uric acid headache, for while in this disturbance uric acid is obviously contracting to some extent the vessels all over the body, it produces special irritation or spasm of an area under the control of the cervical sympathetic.

Suppose that this area of spasm is transferred from the head to the extremities, and we have at once an explanation of Raynaud's disease.

Now, in the *Ophthalmic Review* (March, 1890), Mr. Stanford Morton relates that he saw stasis or thrombosis in the vessels of the retina in one or two patients taking place during an attack of megrim, and there is every probability that these troubles were due to uric acid, and if similar troubles were produced on a larger scale in the extremities we could easily account for all the stages and results of Raynaud's disease.

Further, in one or two cases of this disease which I have had under my care, I have found a greatly excessive excretion of uric acid ; in a severe case, the largest I have ever met with,

giving the relation to urea 1 to 8, that is four times as much as the normal, and in another case, where the attacks were much slighter and never went beyond trifling local pain and discolouration, I had difficulty, as in the case of headache and epilepsy, in finding any excess in the excretion of uric acid, and it was only when the urine of the attack was very carefully separated that I was able to find an excess.

Apparently, then, the excretion of uric acid corresponds with the severity of the attack, and in slight cases uric-acidæmia is temporary and slightly marked, and in severe cases great and prolonged.

Then the remedies of this condition are just such as will affect uric acid; the nitrites, as I have said, raise the acidity and diminish uric-acidæmia and the excretion of uric acid, and in the slight case last under my care salicylate of soda given for some weeks appeared to put an abrupt termination to the attacks. The patient had four or five attacks in the six or seven days preceding the taking of this drug, and more or less frequently for many weeks previously. After it was begun she went twenty days without an attack, and then had but three slight attacks in eleven days, and then no more at all in spite of exposure on several occasions to a temperature several degrees below the freezing point, which had on previous occasions precipitated attacks. I do not wish to lay too much stress on the results in a single case, but taking together all the facts I have mentioned I cannot help thinking that the case for a uric acid causation of Raynaud's disease is rather strong.

If uric acid has such effects in physiology and pathology, as I have been attributing to it, then there is no difficulty in supposing that Raynaud's disease is a result of exaggerated uric-acidæmia.

The coldness of the feet, for instance, in the uric acid headache is often so great that they cannot be kept warm by anything short of sitting with them in hot water, and it appears to me that the difference between this condition and Raynaud's

disease cannot be said to be more than one of degree, and I have never met with a headache in which the excretion of uric acid was so large or the uric-acidæmia probably so intense as in the case of Raynaud's disease above mentioned, so that everything corresponds, and I hope, in some future cases, to be able to test further and more precisely the action of drugs.

As regards the skin, I have no doubt that uric acid affects its functions very greatly by affecting the circulation through it, and that it has important influence in the course of time on its structure, as well as on the growth of the hair and nails, and an influence also in certain skin diseases, such as erythema, so often associated with rheumatism, or the eczema so common in gouty subjects.

And among internal organs I believe that the heart, lungs, brain, liver and abdominal viscera may be influenced to a very important extent, both in function and eventually in structure, through its effects on their circulation, as doubtless every general change in tension and rate of heart beat affects all these organs in the same way and to the same extent as we have seen that it affects the kidneys and their excretion.

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 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 uric-acidæmia.

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 uric-acidæmia, 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 uric-acidæmia, because there is an interruption of digestive and other functions at the end of a period of active nitrogenous metabolism (pregnancy).

In certain conditions of hunger also there is a fall of acidity and temporary uric-acidæmia.

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 uric-acidæmia I shall have to speak very often (see Chap. VII.), 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 uric-acidæmia 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.

(2) Digestive disturbance generally entails a fall of urea and acidity and uric-acidæmia, 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 Chap. II., pp. 64-65, means a fall of acidity and uric-acidæmia.

(4) Circulatory disease may obviously cause uric-acidæmia in several ways.

(5) In urinary diseases, nephritis bulks largely, and of this and its uric-acidæmia I shall speak in Chap. XI.

(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 uric acidæmia, 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 Chap. XI. of the uric-acidæmia 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 nausea, vomiting, or gastric disturbance with secondary uric-acidæmia and its resultant bradycardia.

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 uric-acidæmia, and I shall speak of fatigue in connection with the causation of rheumatism in Chap. VIII.

From the causation of bradycardia by uric acid in accordance with Marey's law we pass without difficulty to the causation of angina (see Chap. IX.), 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 (Fig. 21) 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 (Chap. V., p. 93) 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 uric-acidæmia, 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 Dr. Broadbent ("Pulse," p. 153).

As regards my own pulse, I look upon a fluttering imperfect systole, or a dropped beat, as in Fig. 21, as conclusive evidence of high tension. I have many hundreds of traces of my own pulse, but none show these conditions without accompany-

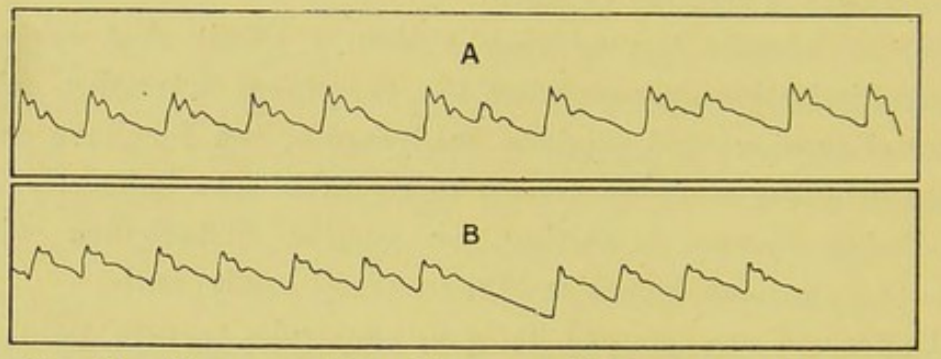

FIG. 21.—PULSES OF HIGH TENSION. (A) FALTERING, RATE 58; (B) INTERMITTENT.

ing (causative) high tension, and I have often produced this condition or removed it in myself and others.

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 Sir Andrew Clark has written about as "arthritic hæmoptysis" may be due to uric-acidæmia and its effects on the circulation) or may be fatal and deadly as a hæmorrhage in the brain.

---

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

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

And when I say that I can not only account for a large number of the above conditions and results of contraction of arterioles, but can, to a large extent, produce or remove them at pleasure, and do so almost every day in myself and others, it will be easily understood that I feel a greater interest in the effects of uric acid on the tension of the pulse than in any other part of the subject.

For it is evident that these effects of uric acid on the vessels must influence the function, nutrition, and eventually the structure of every organ and tissue of the body, and are in this way of infinitely greater importance than anything in the pathology of gout or rheumatism hitherto known to us.

In proof of this I may here just mention shortly a few points. Uric acid contracts the capillaries and arterioles, and their contraction is proportional to the amount of uric acid in the blood. What effects may this produce on the various organs and tissues?

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 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. Several of my epileptic patients have told me that they 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 came 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 Chap. XI.) as being present in Bright's disease.

In the brain we may have slow circulation or stasis as in headache, vertigo and epilepsy, anæmia as in 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 puerperal 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 toxic neuritis may represent the effects of the drug on urates.

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 *B. M. J.*, i. 88, p. 1006, and compare anasarca case in Chap. XI.).

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 some conversion of uric acid into urea as it passes the liver; but it is at least possible that some part of the rise is due to an increased formation of urea, when the metabolic processes in the liver, muscles, etc., are set free from the restraining influence of uric-acidæmia.

Possibly 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 if an hysterical attack is accompanied by high tension of pulse (Broadbent) that may diminish urea by diminishing metabolism, 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. 100). 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.

With regard to muscular metabolism it is interesting to remember that Murchison ("Functional Derangements of the Liver," p. 105) looked upon severe cramp in the legs as a sign of lithæmia, and it is probable that cramp is a sign of some failure in nutrition or in the removal of waste products which might be the result of these circulatory disturbances I am speaking of.

Now uric acid is always acting and is present in more or less excess in the blood in some periods of every day, and if I am correct in my reasoning it is not too much to say that it may eventually be found that it dominates not only function, as I have endeavoured to demonstrate, but that it influences also development, nutrition and decay to an extent which we are at present unable to realise fully; though there can hardly be any doubt that acting over long periods of time its results may be of the greatest importance, and that apart from accidents and infectious disease (though urates account for not a few of the sequelæ of these) uric acid is entitled to the most important position in the study of pathology.

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.

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.

CHAPTER VII.

Mental Depression.

If uric acid affects the circulation in the brain in the same way and to the same extent as we saw reason to believe in the last chapter that it affects the circulation of the kidney and other structures, we stand face to face with a simple explanation of the causation of many cases of mental depression and other functional or organic diseases of the brain.

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 dullness 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 uric-acidæmia; 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.

About two years ago *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 uric-acid-

æmia, 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, vielleight 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, anæmia of the brain. Therefore cæteris paribus anæmia of the brain is 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."

Among the symptoms of incipient melancholia the same writer 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 Dr. Broadbent and others have written.

If, therefore, uric acid exerts on the vessels of the brain the same influence that I have shown that it probably exerts on the vessels of the kidneys and other organs, we shall have anæmia of the brain with mental depression and sleepiness or dulness with uric-acidæmia, and the reverse conditions when the blood is free from uric acid.

Clinically, however, the matter is not quite so simple, for granting that the mental symptoms are due to anæmia of the brain, it is obvious that there may be other causes of anæmia besides uric acid (such as morbis cordis pressure of new growths, &c.), and uric acid itself may produce anæmia of the brain indirectly as well as directly (see *Brain*, Spring Number, 1891, p. 87). Thus the sudden rise of arterial tension produced by the contraction of all the arterioles by uric acid may overpower the heart, which falters and flutters, and finally stops for one or more beats (see fig. xxi.), and down goes the patient in a faint. Here is anæmia of the brain indirectly due to uric acid through failure of the heart, and it is obvious that where the heart is already struggling against valvular disease a relatively small amount of uric acid may overpower it and produce serious consequences.

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 delusion I agree with Dr. Broadbent in believing that there is no absolute line of demarkation (see Croonian Lectures, 1887), and this depression is due, to a certain amount of anæmia of the brain, brought about by the contraction of its arterioles by excess of uric acid in the blood (uric-acidæmia). 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 Chaps. 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. 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 uric-acidæmia are greatest.

Again it has appeared to me that the irritability and bad temper of uric-acidæmia and the cerebral anæmia 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 uric-acidæmia results.

This year May has been a comparatively cold and wet month, and my impression is that murders and suicides have not been remarkably numerous, but I have no doubt that when the warmth of June and July comes to act along with the effects of the recent epidemic of influenza (of the action of which on suicide I shall speak presently) this immunity in May will be more than made up for.

In a word, I believe that the above-mentioned physiological fluctuation in the excretion of uric acid, and the concomitant uric-acidæmia 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 uric acidæmia 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 uric-acidæmia worse than before is produced. From this secondary uric-acidæmia 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. $\frac{1}{6}$th, 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 uric-acidæmia next morning and no necessity to take another dose of morphine.

This experience has led me to suggest the use of salicylate in the attempt to break through the morphine habit. (See Chap. II., 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; 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 uric-acidæmia, 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 uric acidæmia, 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 uric-acidæmia 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 uric-acidæmia.

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 Chaps. II. and III., p. 64), 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 uric-acidæmia results.

Such uric-acidæmia 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 uric-acidæmia, 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 uric-acidæmia 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 (Zects fur Klin. Med., 1890), and others as post febrile bradycardia.

Among cases of pneumonia under my care this bradycardia was very well marked in a strong man who had indulged freely in beer; but was hardly noticeable in a poorly nourished woman who had not so indulged, and the reason of this difference is, I hope, sufficiently clear; the first had large stores of uric acid, the second little. In several papers also I have spoken at great length of the very marked depression that often follows influenza attributing it to a large extent to the above described post febrile uric-acidæmia, and have quoted from a paper read before the Epidemiological Society (*Lancet*, June, 1890, p. 1019), which showed that suicides in France increased 40 per cent. after the influenza of 1889-90, a fact which I should not find it difficult to explain.

Bright's disease again is frequently associated with suicide, and in Bright's disease there is chronic uric-acidæmia, with contracted arterioles and slow high tension pulse.

Menstruation should probably have been mentioned under physiology, but in menstruation there is very often uric-acidæmia because this condition is commonly accompanied with some disturbance of digestion, failure of nutrition, and fall of acidity. I have already (Chaps. IV. and V.), pointed out that women who have fits or the uric acid headache nearly always suffer from attacks at the catamenial period. Dr. 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. 1401), 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.

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 just in the same way that I believe the nitrites act in reducing arterial tension. (See Chap. III.)

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 uric-acidæmia with slow high tension pulse, contracted arterioles in the skin, kidneys and brain, anæmia 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 hyperæmia of 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 capillaries 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 uric-acidæmia. 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 Chaps. II. and III.), and the excretion of uric acid tells us why it does so, for in place of producing uric-acidæmia 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 uric-acidæmia 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 experiences 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 uric-acidæmia 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 of uric acid by 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.

An extremely interesting case illustrating some of these points is published by Dr. Willoughby Gardner in the *Lancet* (1891, vol. i., p. 1311), 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 8th, he attended three long religious services, and took no exercise. On the morning of March 9th 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 uric-acidæmia. 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 uric-acidæmia returns reinforced by the amount retained on the Sunday. This contracts the arterioles, and to some extent overpowers the heart, and partly by contraction of vessels, partly by heart failure, there is produced such severe anæmia of the brain that melancholia with delusions results.

A mercurial purge is given, thus 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 its effects on the cerebral circulation clears up completely. Mercury here acts just 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. 36).

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.

CHAPTER VIII.

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 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 (*Brit. Med. Journ.*, 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," *Proc. of Med. Chi. Soc.*, 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 precipitation 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.

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 the 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. (See p. 96).

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 Chap. II., p. 14).

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 uric-acidæmia 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 Chap. VI. p. 96.)

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 uric-acidæmia. (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), hence, during this period, the excretion of uric acid falls short of its formation, and it is retained and accumulated in the body (see Chaps. II. and III.) (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 uric-acidæmia 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 had 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 indiscrimately given to gouty subjects, are apt to excite paroxysms 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 uric-acidæmia. 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 Chap. II. p. 28), the urea and acidity fall, the retained uric acid is washed out into the blood stream and uric-acidæmia, 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. 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 (*Brit. Med. Journ.*, vol. i., 90, p. 1,241, and fig. xi. 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 in Chap. II. p. 30. 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 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 at the end of Chap. VII.)

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. Bruce 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 uric-acidæmia 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 Chap. VII. p. 135, "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 absolute formation of uric acid and urea, 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 is 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. If a Scotchman comes to England and drinks beer and wine he suffers from gout like the Englishman. Sir A. Garrod says: "The least acid of all alcoholic fluids are geneva and whisky."

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 300 grs. and uric acid about 9 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 much of it was retained in the body, and then, whenever acidity fell from any cause, there was intense uric-acidæmia.

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 uric-acidæmia, and hence I have now complete immunity from the uric acid headache.

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 33, I can see no good evidence of it, and I look upon the excess of urates in the urine as possibly 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 uric-acidæmia 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 uric-acidæmia 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 high coloured and strongly acid." I have pointed out that the urine is scanty in the uric-acidæmia 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 his acidity rules low and the excretion of uric acid is never interfered with. 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 uric-acidæmia 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.

CHAPTER IX.

Rheumatism.

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 *Med. Chi. Trans.* vol. 73, 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 manage-

ment, 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" (*B. M. Jour.*, vol. ii., 1888, p. 10).

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 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 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 health, and can be demonstrated artifically at any time by using drugs which affect the alkalinity (except lithia, see Chap. II.) 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" ("Lumlean Lects., *Brit. Med. Journ.*, 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 "Gout," Chap. VII.) 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 (lumbago) 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.

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 endocardium 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 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 well 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 construction.

And if, as I believe, an excess of uric acid in the blood contracts all the peripheral arterioles and raises arterial tension 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 resistence to be overcome on the mitral valves also; and anyone 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 the 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 (Chap. vii. p. 135) every woman has more or less uric-acid-æmia 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 uric-acidæmia, 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 the process is repeated month after month for years we can easily understand how a microscopic scar becomes

at last a leathery and calcarious 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 uric-acidæmia, 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 uric-acidæmia and its various results.

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 when 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 uric-acidæmia would, for the reasons previously gone into (Chap. II. p. 14), 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 uric-acidæmia at any time, hence the very serious effects of a wetting following close upon these conditions of muscles and skin; and my friend Dr. Eccles, recently 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 speaking of exercise, I will just mention a fact which has interested me considerably, namely, that stiffness and soreness (? slight rheumatism) after severe exercise may be completely prevented by a few doses of salicylate; and the laity, be it remembered, regard these results of exercise as part of the process of growing old; that is, as the circulation through their joints and fibrous tissues becomes less active, and the removal of acids and other waste products of muscular activity less complete, they are more liable to these troubles. 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 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 symptoms 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*, Chap. II. p. 22).

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 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

[1] Wood's *Medical and Surgical Monograph*, February, 1890, p. 355.

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 uric-acidæmia 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 endo-carditis 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. xxii.)

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 17 grs. of urate were formed on this day (in the relation 1 to 33). Therefore about $9\frac{1}{2}$ grs. of urate came from some source other than formation, and probably it was this urate which caused the arthritis, and with its removal and

[1] *Brit. Med. Journ.*, 1890, vol. i., p. 941.

excretion under salicylate there was a marked fall of temperature and amelioration of all the symptoms.

With regard to November 8th 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

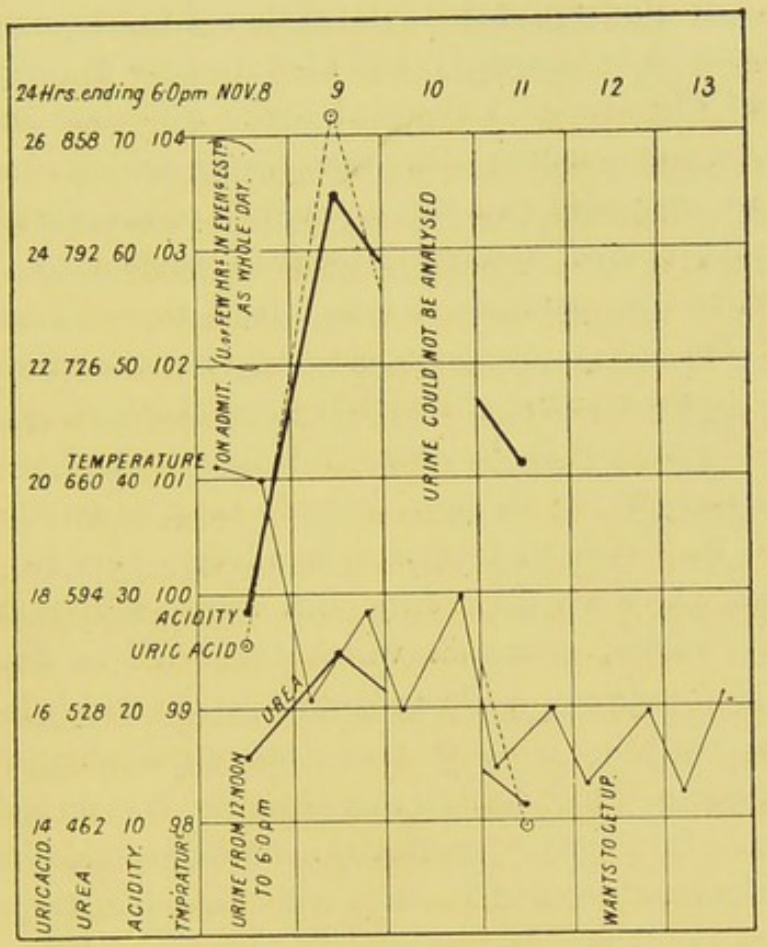

FIG. 22.—SALICYLATE OF SODA BEGUN SIX HOURS AFTER ADMISSION GR. X. EVERY TWO HOURS, FOR SIX DOSES; THEN DROPPED TO EVERY THREE HOURS.

the whole 24 hours could have been collected urate would, no doubt, have been far below urea and acidity much higher.

On November 10th the urine was lost by mixture with another specimen, and on November 11th 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.

Compare this with the excretion of urate under salicylate in physiological conditions (fig. iv.) 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 33 (see my facts and deductions in Chaps. 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. 73).

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.

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 uric-acidæma, anæmia, and debility.

More or less headache and slow high tension pulse are the common signs of this uric-acidæma, and Dr. A. E. Garrod (prev. ref., 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 anything 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 (uric-acidæmia), 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 uric-acidæmia, 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 uric-acidæmia, 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.

[1] *Leçons sur les Maladies par Ralentissement de la Nutrition*, p. 241.

A fever, however, has a double action, for supposing that at the time of its onset there is no uric-acidæmia, 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 uric-acidæmia 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 paper read at Med. Chi. Soc. on "Measles as a Cause of Endocarditis," see *Lancet* i., '91, p. 880) and compare this with my remarks on the effects of measles on the urine in a case of nephritis, Chap. XI. 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 uric-acidæmia 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 uric-acidæmia 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).

There is, I think, evidence to show that the acids of beers and wine, and the excessive formation 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.

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. E. 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 uric-acidæmia 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 33 would be about .09 to .12 gr. per pound per day, in a child of three or four 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 uric-acidæmia 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 formation of uric acid should be very great, and the possibilities of resulting mischief considerable, and that, as pointed out by Bouchard,[1] children fed on meat and meat extracts should often suffer from gastro-intestinal derangements, skin diseases, 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 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

[1] *Leçons sur les Maladies par Ralentissement de la Nutrition*, p. 241.

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 (previous references and Chap. III.), rise of acidity the two things (fever and acidity) being probably co-resultants of increased metabolism.

Young persons then are, from the action of natural causes, often liable to have considerable uric-acidæmia, 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 uric-acidæmia. On this then 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 uric-acidæmia 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 recently 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, 2in. 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 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.

P.-M. 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 oz. 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.

P.-M. September 22, 1888.

Body somewhat emaciated, rigor absent.

Heart. 18½ ozs. Left ventricle hypertropied. 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 oz., nutmeg with fatty degeneration.

Joints. Copious deposit of urate and 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. age 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 creps 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.

P.-M. May 26. Pleuræ a few old adhesions both sides.

Heart. 12 oz., substance firm. Aortic cusp of mitral valve slightly thick.

Lungs. Right 23 oz. Left 22½ 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.

And 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 from 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.

CHAPTER X.

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.

I shall limit myself, however, in this chapter to a statement of the facts, and a few remarks as to their possible meaning without going very deeply into theory, as I have no doubt there is still a great deal to be learned as to the causation of the disease.

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 (*Brit. Med. Journ.*, 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 treatment 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 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 quotations 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 (prev. ref. 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 (*Brit. Med. Jour.*, 1883, vol. i., p. 863-866) credits diabetes to a vaso-motor paralysis of the chylopoëtic 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 urates 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 uric-acidæma 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 (uric-acidæmia) 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 diæthesis may be thus summed up: heartburn and eructations, oppression, and frequently sleepiness after food; a feeling of distension 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.

So that glycosuria is generally contemporaneous with uric-acidæmia and congestion of the liver, what is the relation of congestion of the liver to uric-acidæmia? Can uric-acidæmia produce congestion of the liver and through this glycosuria or diabetes?

Now Dr. W. M. Ord has pointed out (*Brit. Med. Jour.*, 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 inversely as the uric acid that is circulating in the blood, therefore uric-acidæmia will cause high tension, and this will produce congestion of the liver and glycosuria.

The causation of glocosuria is thus theoretically complete, and it corresponds with the experience of clinical observers that it alternates with gout and corresponds with the absence of gouty arthritis, that is with uric-acidæmia.

I may say also that my experience corresponds absolutely with that of Sir A. Garrod, and that in my own case congestion of the liver always corresponds with uric-acidæmia, 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.

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 (prev. ref. 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 uric-acidæma 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 uric-acidæmia than gastric catarrh, 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 uric-acidæmia 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 uric-acidæmia 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 uric-acidæmia, 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 (see Chap. VI.).

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 (uric-acidæmia).

I have shown that uric-acidæmia 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 uric-acidæmia) 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 uric-acidæmia; and supposing that the uric-acidæmia 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.

My object is to point out the relationship of glycosuria and possibly diabetes to gout and uric-acidæmia, but I shall not at

present attempt to choose between the various ways in which uric-acidæmia may act.

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 uric-acidæmia, 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 (p. 138).

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 uric-acidæmia, 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. Barth. Hosp. 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 Contrexville, 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.

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 und watery; but acids, sulphates, and salicylates also, as we have seen Chaps. 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, 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 38) 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 associated 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.

My cases treated by salicylates have, except the last one, been given in full in the paper in the "Hospital Reports" just referred to, and considerations of space oblige me to give them here very shortly.

January, 1888.

Mary A. D., æt. 55.—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.

May, 1888.

Mrs. C. æt. 45.—Urine 1032-1040 and containing five 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. 20). 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.

Nov., 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.

Feb. 16th, 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 Feb. 26th, 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 uric-acidæmia, and also interfered with the full action of the salicylates.

Henry F., æt. 54, *Nov.*, 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 uric-acidæmia; 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 uric-acidæmia 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.

The preceding cases may be classed as glycosurias, but the two following cases are severe ones, and tend rapidly to a fatal ending, whatever they may be called. In one of them, as will appear, salicylates and all other drugs failed to cure, though even here salicylates did better than anything else.

Jane B., æt. 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. 1st, 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.) (See also p. 188.)

She did not come again till Aug. 17th 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 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. 7th, 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.

My last case is that of Winifred H. F., age eight years, who was admitted under my care at the Royal Hospital for Children and Women, January 22nd, 1891.

Complained of thirst and nocturnal urination: pale, wasted; weight 2 st. 5 lbs. Some increase of liver dulness, and constipation.

Urine 2220cc. 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 9th 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 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 12th.—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 18th urea was to sugar 1—3.2, and on the 19th 1—3, and on 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 28th 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. $\mathfrak{m}$x. given four times a day with the salicylate.

March 26.—Going on much the same, but there is occasionally some vomiting, and the diarrhœa 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 19th (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.

Frerichs says that salicylates reduce sugar by interfering with digestion; but even in this case they reduced sugar relatively to urea, and interfered with nutrition and digestion less than codeina, and in the previous 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*, Aug. 1891).

I am aware that all this, even if my facts and inferences are

correct, touches only the fringe of a great subject, but the value of salicylates in treatment is not as yet sufficiently known, and I hope that the gouty connections of glycosuria and diabetes, which are in themselves of great interest, may eventually help us to obtain a more accurate knowledge of its causation.

CHAPTER XI.

Bright's Disease.

Bright's Disease, like diabetes, has some interesting connections with gout and uric acid, some of which are definite and distinct, while others are indefinite or doubtful; and though a consideration of all connections is interesting and suggestive, it cannot be said to completely clear up the causation of the disease.

In a paper on "The Connecting-link Between the High-tension Pulse and Albuminuria" (*Brit. Med. Journ.*, 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 have never seen any reason to alter my opinion, and I propose here to carry the same suggested explanation a little further, and for this purpose I will first shortly recapitulate the chief points of my 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 prealbuminuric 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.

After what I have said in previous chapters it will easily be understood that further investigation has tended to greatly strengthen my opinion with regard to this point.

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 (hetro-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-albumiæmia) 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-Lagrave says (prev. ref. 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 Chap. VI., p. 122, the way in which uric-acidæmia by interfering with the circulation in the liver, muscles, skin, &c., may hinder metabolism, and lessen the formation of urea, hetero-albuminæmia, and hæmo-globinæmia being results of its continued action.

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 in-

jected into a dog, and this albuminuria will be proportional to the amount of diffusible albumen in the blood injected.

Labadie-Lagrave (prev. ref. 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, alcoholism, 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 and 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 (uric-acidæmia).

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 uric-acidæmia, namely, Raynaud's disease.

I shall now bring forward further evidence on these points, showing, I think, that while the theory of primary kidney lesion will not account for all the facts, the theory of hetero-albuminæmia which may be, in part, the work of uric acid, will probably account for them completely. I shall also shortly give notes of one case of Raynaud's disease, one case of paroxysmal hamoglobinuria, and one case in which both these functional disturbances occurred together; also my results regarding the excretion of uric acid in the attacks, and the effects of treatment from the point of view of their causation by uric-acidæmia.

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.

Another point in Dr. Mahomed's writings which has interested me greatly is his description of certain clinical conditions he met with in the case of Weston the pedestrian, and his remarks upon them (*B. M. J.*, March, 1876).

Thus he narrates that after walking 244 miles it was found that the tension of the pulse had decidely increased, he steadily lost weight during several days to the total extent of $5\frac{3}{4}$ pounds, was sleepy and complained of feeling cold; on the third day at 10 a.m. Dr. Mahomed says, "on this occasion a marked alteration was discernible in the pulse. The tension was now very considerably increased, this is indicated by the prolonged sustention of the tidal wave and the height of the aortic notch from the base line ———. The second sound of his heart was accentuated and the first a little prolonged." The temperature later

on fell to 98.4 (his normal temperature being 99) and Dr. Mahomed remarked with regard to this, "The falls of temperature which had been previously observed during his walks by Dr. Austin Flint, jun. and also by Mr. Thompson, were most probably due to a similar alteration in his arterial tension."

Every symptom here recorded has an immense interest for me: thus Weston steadily lost weight for several days to the total extent of $5\frac{3}{4}$ lbs.: with this no doubt there was a fall of urea and acidity, even if his appetite did not fail with his energy and power of keeping awake, and as a result the blood was flooded with uric acid, and excess in the urine would have been found if looked for.

All the other symptoms were the results of this, the high tension pulse of which Mahomed so well describes all the signs and symptoms, the sleepiness, the cold surface, the further fall of temperature, they are but the signs of a slight migraine, all of which, as I have pointed out, I can produce at pleasure: and then mark what occurred next day. "During the first part of day he had been tired and sleepy" (uric-acidæmia of the alkaline tide) but after two hours' sleep "he awoke (1 p.m., end of alkaline tide) 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," which, as shown by the traces, had again become normal; he quickly regained the weight he had lost, increasing as much as 5 lbs. in twenty-four hours, on the second day of normal tension (*i.e.*, with relaxation of the vessels active metabolism returned; and this is a good illustration of the effects of high tension on nutrition).

I can produce just such alterations in pulse tension in anyone by affecting uric acid; but the point of greatest interest with regard to the causation of albuminuria is yet to come.

At the time of Mr. Weston's threatened break-down Dr. Mahomed expected to find some albumen in the urine, but none was found, as he says, "The urine throughout, Dr. Pavy informs me, has continued free from albumen; nor at the time of high tension did it give any reaction with the guaiacum test for

blood." Probably the good care which Mahomed took of Weston in the matter of rest and blankets prevented his breakdown from being complete, and also prevented his having albuminuria; but one of his competitors, James Taylor, was not so fortunate; of him Dr. Mahomed says, "A good example of failure from this cause [dilatation of the heart from high arterial tension] was seen in Taylor, one of Weston's competitors during the late match. A tracing of his pulse is represented by No. 10; it clearly indicates a dilated and failing heart, the systole is prolonged, the tidal wave being too much sustained, while the impulse is feeble, the upstroke being short and somewhat oblique. Although it felt to the finger extremely small and feeble, nevertheless it required 4½ ozs. of pressure to develop the tracing completely. At the time when this was taken he was cold and much distressed. Early on the third day after completing 122 miles he was compelled to desist; his pulse was then described as being almost imperceptible. This, then, was an evident case of failure from dilatation of the heart, and must inevitably have been preceded by high arterial tension. Unfortunately he was not under regular observation, and his urine was not examined; it would most probably have been found albuminous."

I may say here that the pulse trace does not appear to me to show great failure of the heart, such as would lead to congestion of the kidney and albuminuria. It shows very high tension, *i.e.*, great contraction of the arterioles, but the heart was not very weak, as Dr. Mahomed tells us that 4½ ozs. of pressure were required to develop the tracing.

The exact view that Dr. Mahomed held with regard to the causation of this form of albuminuria is not very clear from the context, but in "Guy's Hospital Reports," 1879, p. 365, we find him saying, with regard to the causation of Bright's disease, "I have tried to show . . . that a poisoned condition of the blood is the primary condition, that this produces an impeded circulation through the capillaries and subsequently the cardio-vascular changes; while the bad blood produces a congestion

of the excretory organs, that is, of the skin, mucous membranes and kidneys, but especially of the latter, and that it depends upon the nature and intensity of the blood poison whether this congestion is chronic or acute."

Dr. Mahomed probably thought, then, that, the albuminuria he expected in the case of Weston's competitor, Taylor, might be due to the irritation of the kidney by the poison which contracted the arterioles and produced the high tension.

Taking it that this poison was uric acid (because I can show that uric acid will produce these arterial changes), the question arises, Does uric acid irritate the mucous membrane of the kidneys and produce albuminuria or acute and chronic nephritis, according to its quantity in the blood and the duration of its action upon them?

And there is no doubt that some would seek to explain the above albuminuria occurring during temporary high tension, as well as that in other so-called functional albuminurias, as due to heart failure.

We have thus, then, 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).

Again, in the "Guy's Hospital Reports" of 1881, we find Dr. Mahomed speaking of cases of nephritis, and also of convalescence 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 *B. M. Jour.*, 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 discrasiques* 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.

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, the vessels, and the heart, may interfere in the way sketched out in the previous chapter on diabetes 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 Chap. VI., p. 122.)

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 (*B. M. Jour.*, 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 as can be seen (Chap. VI. and XI., figs. 1 and 16), 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 benefits of a night's rest and recuperation.

Again, in 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? It may be argued that the uric-acidæmia which I have shown is greatest after breakfast for physiological reasons, raises the tension, overpowers the heart, and so produces or increases congestive albuminuria; but I have already said with regard to Mahomed's case (Taylor) that though I do not doubt the effect of high tension on the heart, and that it may be, and often is, very serious especially in old people or those who already have morbus cordis, I have doubts whether in the cases mentioned the effect on the heart in young and otherwise healthy people was so great as to account for congestive albuminuria.

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 uric-acidæmia 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 uric-acidæmia 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," 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 uric-acidæmia 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, prev. ref., 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 the two causes, (1) the effects of contracted arterioles on the nutrition of the kidney, and (2) the irritant effects 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 uric-acidæmia in old age or other failure of nutrition; and this uric-acidæmia is to my mind the cause of the chronic nephritis so often found in the *post-mortem* room with chronic gout.

But where the uric-acidæmia 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.

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 heteroalbuminæmia 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.

I shall now narrate some cases bearing upon the effects of uric acid on the blood cells, both in anæmia and in paroxysmal hæmoglobinuria.

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 (uric-acidæmia).

His water on the day after the attack is quite clear again.

December 10.—His mother brought him to my out-patients' to-day saying that he has an attack coming on. Has been taking cod-liver oil and steel wine for the last week.

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; showed the spectrum of oxy-hæmaglobin, 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 uric-acidæmia; 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 oxyhæmoglobin 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.

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 also pointed out in my previous paper 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. 1st and a pain in his right side on Aug. 7th. 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. 17th, 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 was due to uric-acidæmia, 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 uric-acidæmia, for which I might be able to do something.

On Sept. 26th 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. 30th 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 soda salicyl. gr. x., sp. am. arom. ℥xv., three times a day after meals, with the object of affecting the uric-acidæmia.

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. 7th, 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. 10ozs.

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. 13lbs.

Nov. 26.—Acids and salicylate begun again.

Nov. 29.—Red cells 35 per square. Spleen 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.

Another case bearing on these points is that of Margaret C., aged 3 years, who came among my out-patients Sept. 23rd, 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. Again an enormous excess of uric acid, but there is no albuminuria. Given a little dilute nitro-hydrochloric acid and ɱi. of Tinct. opii twice a day.

Sept. 26.—Going on well; urine of this day gives a relation, uric acid to urea 1—20.7.

Sept. 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.

Sept. 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.

The last case I shall mention is one which I have published in full elsewhere (Paper read at the Medical Society, Dec. 7th, 1891).

Eliza H., aged 5.—Under my care at the Royal Hospital, Waterloo Road. Paroxysmal hæmoglobinuria and Raynaud's disease. In this case the hands were the parts generally affected, becoming cold, blue and painful; but this passed off in a short time. She had many attacks, the more severe ones being followed by rise of temperature and hæmoglobinuria.

I estimated the uric acid urea relation on several occasions, and often got very considerable amounts of uric acid as 1 to 17, but as the attacks were often short there was generally admixture of urine before, during and after in the bladder, and the results did not come out so clearly as in the more severe attacks of local asphyxia in the previous case of Margaret C., aged 3 years. Urine containing hæmoglobin gave relations of 1 to 22 up to 1 to 30, but it was often quite impossible to separate the excretion accurately.

There is a point of interest with regard to the local asphyxia —namely, that when later on I put her on salicylate of soda with a little nux vomica, the attacks suddenly ceased to appear though she had had several in the week before the drugs were changed, and her temper, which before had been very bad, improved wonderfully (removal of uric-acidæmia). She had no attack till twenty days after the salicylate was begun, and after that she had three slight attacks in eleven days, and then they ceased altogether, in spite of exposure on the roof of the hospital on several occasions to a temperature of 26° or 27° Fr. and in spite of washing her hands in cold water, which had previously appeared to excite attacks.

With regard to the Raynaud's disease I can, as I have shown, alter arterial tension at pleasure by affecting uric acid and the cold surface, and extremities in migraine are but a minor condition of the first stage of Raynaud (local asphyxia). I have no doubt, therefore, that the trouble in these cases is due to uric-acidæmia and varies with its intensity as shown by the excess of uric acid in the urine when it can be accurately separated; but as in the case of headache and epilepsy the uric acid excites a special influence on certain vascular areas, either because of certain anatomical or physiological conditions, or its influence may be determined by local exposure to cold, so that in the case of Eliza H. we have the uric acid affecting specially the hands owing to their exposure to cold water or cold air.

So far as I know, Raynaud's disease, or conditions practically indistinguishable from it, are often met with as sequelæ of an acute fever, as measles, scarlet fever, etc., and we have seen in Chaps. V. and VI. the way in which fevers bring about uric-acidæmia with mental depression, scanty urine, slow pulse (post febrile bradycardia) and other symptoms, of some of which Raynaud's disease is, from my point of view, a mere exaggeration. I also mentioned, in Chap. II., the occasional production of hæmoglobinuria by quinine, and suggested that it brought about this result by producing uric-acidæmia, which I showed is the result of giving quinine even in physiological conditions, and much more so in malaria, where the spleen is large.

The association of these conditions with hæmoglobinuria is very interesting, and if I am right in suggesting that uric acid causes destruction of red cells, the explanation is very simple. We have a slight uric-acidæmia interfering with the function of the liver and skin, and causing hetero-albuminæmia which, if severe, may cause albuminuria; and we have a more severe uric-acidæmia causing not only hetero-albuminæmia, but also destruction of blood cells and hæmoglobinæmia, especially if its action is aided by cold applied to the skin.

I have given above my reasons for believing that uric-acidæmia is a cause of anæmia; but if uric acid does in this way produce hetero-albuminæmia and hæmoglobinæmia, it brings about what is possibly the first stage of Bright's disease.

I may point out that the view that uric acid is a cause of anæmia, furnishes a simple explanation of the anæmia of Bright's disease, in which v. Jaksch has shown that there is excess of uric acid in the blood (and the high tension pulse needs no demonstration), of rheumatism in which after the acute attack is over, there is uric-acidæmia and high tension pulse; and the anæmia and cachexia of malaria obtains a similar explanation; for in cases where the spleen is large, the blood is continually flooded, from time to time, with excess of uric acid, as I have pointed out elsewhere (*Brain*, Spring Number, 1891, p. 73; see also splenic leucocythæmia case above given), while the anæmia of young women may find its explanation in the uric-acidæmia of menstruation, which is a potent cause of suicide (see p. 136).

Some points have been mentioned by writers on these subjects, which will, I think, be seen to have an important bearing on the possible causation of these disturbances by uric acid.

Raynaud showed that the disease he described, was due to spasm, and that there was no obstruction, or disease of the vessels; and in some of these cases, affections of sight, with narrowing of the retinal arteries, have been recorded; also epileptic attacks in the same connection, the explanation of which I have already gone into. Changes in the nerve trunks have been noted; but I think that these are probably effects of the uric-acidæmia, and not the causes of the Raynaud attacks. It is also pointed out (*Lancet*, vol. ii., 1889) that Raynaud's paroxysms may be worse in hot weather, and are met with even in India; and this may be correlated with the excessive excretion of uric acid (and uric-acidæmia), which I have shown takes place in the warm season.

An extremely interesting case of paroxysmal hæmo-globin-

uria was recorded by Drs. Bristowe and Copeman, (*Lancet*, vol. ii., 1889). The attacks were brought on by exposure to cold; but the temperature was subnormal before exposure to cold; then the patient had shiverings, just such as I have had in severe attacks of migraine, and such as I have described in the case of G. F. T., and later his temperature, as in this case, rose to 102° or more.

It is said, that in pernicious anæmia there is excessive destruction of red cells in the portal system, but the liver disposes of the hæmoglobin, so that it does not appear in the urine; but in hæmoglobinuria there is destruction of red cells in the systemic circulation. The first may be due to the effects of uric-acidæmia on the liver, the second to its effects on the metabolism of the skin.

In paroxysmal hæmoglobinuria and albuminuria, there is said (*Lancet*, vol. ii., 1889, p. 307) to be no disease of the kidneys; true, but the kidneys may become diseased if the albuminuria is continued (Semmola). Several writers have described a form of hæmoglobinuria which precedes Bright's disease (*Progrès Medicale*, September, 1889, p. 253), and others again say that acute nephritis may be preceded by hæmoglobinuria (*Lancet*, vol. ii., 1889, p. 1007), and all this is greatly in favour of my suggestion, that a less severe condition of uric-acidæmia may produce hetero-albuminæmia, albuminuria, and nephritis.

Again it has been recorded (*Lancet*, vol. ii., 1889, p. 1086) that attacks of hæmoglobinuria may be followed by marked diuresis, and this has been attributed to the diuretic action of hæmoglobin; but a knowledge of the action of uric acid on the arterioles affords, I venture to think, a more simple explanation. I have pointed out that urinary water varies inversely as the uric acid excreted along with it, that in uric acidæmia it is scanty, and when the blood is cleared of uric acid it becomes profuse. Now hæmoglobinuria, I am suggesting, is the result of severe uric-acidæmia; but when the temperature rises and the attack comes to an end, the blood is cleared of

uric acid, the arterioles of the kidney are once more able to relax, and a more or less profuse diuresis is the result.

Besides, it is by no means extraordinary, that a substance like uric acid, which exerts such a powerful influence over the vessels should, directly or indirectly, exert some influence on the blood and albumens they contain.

The attack is followed by a great fall in the number of red cells in the blood, a fact which was well illustrated in one of my cases, Eliza H.

Doubtless other substances besides uric acid will cause destruction of red cells; and no doubt also, the condition of the red cells will hinder or prevent, or on the other hand, aid and increase its destructive action. Is it not probable that the condition of the red cells and of the other circulating albumens is largely influenced by the completeness, or otherwise, of the metabolism in the liver and skin (Semmola), which again is under the influence (as I have suggested) of uric acid?

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 uric-acidæmia; and this author himself points out, that in functional albuminuria there are frequently bilious attacks, which I should translate by the one word uric-acidæmia. 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; but there was severe uric-acidæmia, and treatment of this was followed by general improvement. Several writers have suggested that

bile salts affect the hæmoglobin (Macmunn, *B. M. Jour.*, 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 uric-acidæmia.

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 of 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 (Chaps. 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 also 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 uric-acidæmia 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 uric-acidæmia, 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 recently 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 kidneys; the result was a copious diuresis and removal of the dropsy. Now, precisely the same can be done with drugs, acids, opium, mercury, any of those in Chap. 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. 20, p. 100), 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?

In chronic nephritis you have changes both in the vessels and general tissues of the kidney which probably allow it to react differently to uric acid and the contraction of vessels it produces; but even in chronic nephritis the same laws hold to a considerable extent. I have suggested, as the result of my own observations on the matter, that in chronic nephritis the uric-acidæmia 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—uric-acidæmia 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, prev. ref. p. 15).

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 uric-acidæmia is relatively less severe.

Uric-acidæmia 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 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 low as 40 (intense uric-acidæmia). 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 pp. 93 and 114) as occurring in migraine.

We have here, then, as I have shown, all the causes which produce uric-acidæmia; and all the signs of its presence and, further, all the drugs which do good in treatment (opium, acids, etc.) 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 "Epilepsy," Chap. V.).

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 (uric-acidæmia) and then some rise of acidity precipitates it on the joint, and though both troubles appeared to get worse together the increase of albumen may have been due to the uric-acidæmia 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.

Another and perhaps a better explanation of this case may be afforded by supposing that the excess of albuminous food (meat) increased his hetero-albuminæmia and albuminuria, and this, according to Semmola, would increase the kidney irritation. This latter would, in accordance with my reasoning, diminish the alkalinity of the kidney, prevent the excretion of urate, and cause it to be retained in the body, increasing the uric-acidæmia, and some of this excess might then very well be deposited on the already damaged structures, periosteum and joint, increasing their irritation; and thus we get a contemporaneous relapse of both renal and arthritic troubles due to a temporary excess of albuminous food.

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.

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-albuminuria 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 (uric-acidæmia) might actually produce the excessive diffusibility of albumens (hetero-albuminæmia) and the secondary fall in the formation of urea (see pp. 122); thus forming the "connecting link" between the "prealbuminuric 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 uric-acidæmia, 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 uric-acidæmia 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, 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 albu-

mens to be metabolised by the damaged organs (liver and skin), or increase the formation 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. 100), then the anasarca of Bright's disease may be a mere exaggeration of what occurs in physiological conditions.

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 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 in this and the previous chapter, 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 glycæmia and glycosuria, and under others, hetero-albuminæmia

[1] *Archives de Physiologie*, 1883.

and albuminuria. The secondary result in each case being some kidney irritation, which, in the case of the albuminuria, may according to Semmola, go on to the production of the structural changes met with in nephritis; though no doubt the uric-acidæmia, by its effects on the circulation, contributes something to the structural alterations found in all the organs and tissues after death.

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.

CHAPTER XII.

Treatment.

If my facts are what I believe them to be, and my deductions from them are moderately correct, the main indications for treatment have at least the merit of simplicity.

If high arterial tension, headache, epilepsy, mental depression, and various functional and organic troubles resulting from high tension more or less directly, as Raynaud's disease, glycosuria, albuminuria, hæmoglobinuria and anæmia are due to excess of uric acid in the blood (uric-acidæmia), while arthritis, endo- and pericarditis, and various irritations and perversions of nutrition in fibrous tissues are due to local excess and deposition of urate, then obviously our very first duty is to diminish the urate in the body generally and the blood specially, and the only remaining question is as to the best means of doing this.

If uric acid is, under any conditions whatever, formed in excess—that is to say, in excess of the relation to urea of 1 to 33 (that is, one of uric acid for thirty-three of urea)—then it is our duty to prevent such excessive formation by any means in our power; but if, as I have suggested, uric acid is never formed in excess of this relation but accumulates in the body because some of the urate so formed fails to be excreted while the more soluble urea is fully and completely excreted, then what we have to do is first of all to clear the body of the urate that has accumulated and been stored in it, by means of solvents such as salicylates, alkalies, phosphate of soda, etc., and then to reduce the whole nitrogenous metabolism by reducing the income of nitrogen, so that the formation of uric acid along

with urea shall be permanently reduced, and as the acidity falls with the urea (see p. 24) the solubility of the uric acid is but rarely interfered with, and there is but little likelihood that any of it will fail to be excreted and so be retained in the body.

Before going further, there is one good old fallacy—the offspring of imperfect observation—to which I must again devote a little attention.

Several years ago (*Brit. Med. Journal*, vol. ii., 1888, p. 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.

Undoubtedly the first effect of animal diet is to diminish the excretion of uric acid because it raises the acidity, 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 nearly the equivalent amount, and the plus excretion on vegetable diet would gradually have fallen towards the level of formation—1 to 33—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, only on animal diet part of the urate formed 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 uber 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, but excretion falls short of formation owing to rising acidity, and some part of that formed 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.

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—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 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.

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. I have previously given the figures of excretion (p. 69,) and it will only be necessary to say here that in reducing my urea formation to three-fifths or one-half of its former level, I have diminished to a corresponding extent the formation of urate, and at the same time by diminishing acidity have removed the chief obstacle to its free excretion; for these two reasons I have now never any excess of urate in my blood, and am practically free from the pain and misery it used to entail.

Such a result must speak for itself even if the theory on

which it 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 this reduction of 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, and I am not without experience of other diet, as from twelve to eighteen years ago I used to go in for a great deal of muscular exercise, and, according to the theory of the time on training, ate three meals a day, of which meat was by far the most important constituent.

My headaches were then and afterwards extremely severe, and I look back upon that time with regret, as I have no doubt that this excess of nitrogen did injury to the structure of many important organs and tissues which no subsequent change of diet could wipe out.

The treatment, then, of all these diseases is to reduce the nitrogen and run down the urea to three-fifths or one-half, or even less, of its original volume. Take the urea for two to three weeks under ordinary conditions of diet—take this as your standard and steadily reduce it, watching nutrition, weight, and general health to see that no harm is done by going too quickly.

How far urea may be reduced with advantage is a point that remains to be worked out, and I am still experimenting on it in my own case. It is said in Pfluger's *Archive* (vol. xli. p. 533) that a healthy adult can maintain his weight and nitrogenous balance on 30 to 35 grms. of proteid=5.8 grms. of nitrogen. I have therefore not yet reached anything like the minimum possible.

Professor Humphry says (*B. M. Jour.*, 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 alter the 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.

So much for general principles. We are now in a position to take the treatment of the special conditions.

With regard to arterial tension, it is clear that the less urate there is in the blood the lower it will be; that when there is little or no headache, in which the tension is very high, the tension as a whole must be lower than when headaches are frequent and severe; and my experience is in complete accord with this reasoning, though, as there is no very accurate mode of measuring tension, it is not very easy to say by how much it is higher or lower.

Marey's law is that pulse rate varies inversely as arterial tension—hence pulse rate is, to some extent, a guide to tension; it is at best, however, merely a relative guide, useful only for one and the same person, and under similar conditions.

For instance, if a person with temporary high tension has a pulse rate of 56 to 60, and the tension is pretty quickly reduced, the pulse will quicken to 68, 70, or more; but if the tension is permanently reduced to the same point it may not keep up the rate of 70, and may fall to 56 or 60 with less tension and less

urate than it did formerly, when the general level of tension was higher. You cannot, therefore, say with any pretence to accuracy that one person, with a pulse of 56, has as high tension as another person with a pulse of the same rate; in both probably the rate will quicken as you reduce tension, and will slow as you increase it, and for any given case the rate is proportional to the tension, and is a relative guide.

The treatment of more or less chronic high tension, when not associated with organic disease, and due to functional uric-acidæmia is the clearing the blood and body of all the urate they contain and the reduction of formation for the future, by reducing the income of nitrogen.

As regards the immediate treatment of the high tension, when it is important for any cause to reduce it at once, this may be done by means of any of the drugs which clear the blood of uric acid (Chaps. II. and III.).

The most quickly acting of these are the nitrites, but their effect also passes off most quickly; if, however, they are followed by opium, acids, or mercury, a reduction of tension lasting a good many hours may soon be produced. As to opium, ♏v.—vii. of the tincture may do very well, or $\frac{1}{6}$ gr. of any salt of morphine; as to acids, dilute nitrohydrochloric, sulphuric, or phosphoric will do—say ʒss. in half a pint of water, this quantity to be gradually consumed in the course of one-and-a-half to two hours, and after that ♏x. three or four times a day according to circumstances.

As to mercury, it is not necessary, and indeed not desirable, to give purgative doses; gr. $\frac{1}{2}$ of calomel twice or three times a day will do quite well (see fig. 11), and if this produces the least intestinal pain or tendency to relaxation of the bowels, a little morphine should be given along with it; they do not interfere with each other's action, but quite the reverse.

Another way of affecting tension is to give acids and salicylates, and this has the advantage that it not only clears the blood of urate, but that this urate, instead of being stored up and retained in the body, as is the case when acids, opium,

or mercury are given, is removed from the body as salicyluric acid, and excreted, so that it will never be the cause of any trouble in the future. A good way of carrying out this treatment is to give ♏x.—xv. of a dilute acid well diluted, just before meals, and grs. xv.—xx. of salicylate after meals three—or if necessary four--times a day.

I am here speaking of high tension apart from organic disease, such as Bright's disease; but it was with this treatment by salicylates and acids that I altered the pulse rate and tension in the case of Bright's disease, of which the traces are given in fig. 20, and the patient improved, and the albumen diminished while on the drugs.

As regards headache, any of the drugs above mentioned, that clear the blood of urate and reduce tension, will also improve or cure the headache, and they may be used in just the same way.

I more frequently make use of acids or opium, but any of them will do; the only point to remember is, not to give anything that will put the stomach out of order, or increase nausea, if present; for this reason salicylates should not be given when there is any nausea, as they will increase it, and possibly put out the digestive process so much that all absorption will cease, and obviously, if they are not absorbed, they cannot affect the urate in the blood.

I generally treat an attack on the following plan: if it is slight, take a small dose of opium or acid, whichever is at hand, sit quiet, and get the feet warm. If the attack is more advanced and severe before it is possible to begin any treatment, the feet may be put in hot water and kept there for some time, and warm wraps, and a chair in front of the fire should be used. In my own case, as I have said, sitting vertically upright, with the face turned up to the ceiling, greatly relieves the pain, and in most cases, I think that the horizontal position makes it much worse.

Food may be taken as usual, if there is no nausea, and a little wine (sherry, or champagne) will do good, as it acts as an

acid, and tends to dilate the contracted vessels. The only point about food is, as in the case of drugs, not to produce or increase nausea; as this will, in the way I have mentioned, do harm, and make matters worse.

If the headache improves with these measures, keeping quiet and warm for a few hours will probably complete the cure.

If, in spite of these treatments, it gets worse, this is almost certain to be due to some rather more serious disturbance of digestion, to which will presently be added nausea and vomiting; the uric-acidæmia is actually due to the gastric upset, as urea and acidity run down from failure of absorption, and with increasing alkalinity of the blood, there is sure to be uric-acidæmia (unless, as we shall see later, the body has been previously cleared of urate, and its formation reduced by diet).

Under these conditions, it is useless and impossible to treat the urate, and we must get the stomach into a condition to digest and absorb, before we can hope to do anything with drugs by the mouth. If the headache is really severe, a small injection of morphine is probably the best thing, and then treat the stomach; and a simple and useful remedy is, I find, a tumbler or two of hot water at the temperature of hot tea, preceded or accompanied by a small mustard leaf on the epigastrium for twenty-five minutes; if these fail to remove the nausea, the best way is to take more warm water, but not so hot as that first taken, so as to promote vomiting, and clear the stomach in this way; and when this ceases, follow by a good dose of Hunyadi Janos, or other aperient water containing sulphates.

In this way, the stomach and intestines are cleared, and got into a condition to digest and absorb as quickly as possible; food can then be begun again, and a little acid and nux vomica can be taken before it.

In my own case, I now know pretty well the causes which will produce a sufficiently large urate fluctuation to cause a head-

ache, and I can, therefore, go in for prevention. Thus, when I have had several dinners or suppers in the same week, and see my urea and acidity running up, I know very well what will happen, as they come down a few days later; I, therefore, take gr. xv. of salicylate three times a day, for two or three days, and, by thus preventing the urate accumulation I prevent the unpleasant after-effects.

A single day of exercise in the open air, as riding, cycling, boating, &c., often has the same effect, it runs up urea and acidity for the time, and as they fall, there will be uric-acidæma; and here, again, a few doses of salicylate while the acidity is high, will prevent this and its results.

So much for the treatment of the headache attack; but after all there is no treatment to compare, as regards success, with the prevention, which results from reducing nitrogeneous metabolism. If there is little or no urate in the body, falling acidity will be unable to produce uric-acidæmia, and will do no harm, and this is the means by which, in my own case, I have obtained immunity.

Epilepsy, in so far as it is due to uric-acidæmia, differs from high tension pulse and headache, in that the attack gives little or no warning of its approach; we are therefore limited in treatment to prevention or attempt at prevention when there is any warning; to attempting to stop a series of attacks when from previous experience such appears probable; or to relieving the heaviness and stupor which may follow an attack or series of attacks. This is practically the treatment of symptoms, and the real treatment of epilepsy is that which by diet aims at reducing the quantity of urate in the body.

I have previously pointed out that a considerable number of cases have been put on record in which a milk or farinaceous diet has appeared to do good (see Broadbent: Croonian Lectures, 1887; L. C. Gray, *New York Medical Journal*, July, 1884, and Jackson's "Letters to a Young Physician," p. 66-67). I have also recently heard from Dr. J. Ferguson, lecturer on nervous diseases in the University of Toronto, that he has for

some time advocated the "dietetic treatment of epilepsy" (see *Therapeutic Gazette*, Dec., 1890), and he concludes his paper as follows: "The clinical facts remain whether the explanation stands or falls. Patients that have been greatly afflicted with epilepsy and have become wearied with much taking of drugs, have derived a very great deal of good from being restricted to a diet containing the least amount of nitrogen consistent with life, and that, too, almost exclusively of a vegetable kind."

I think that it is of interest also in this connection to remember a fact of which I have had a good deal of clinical experience, that those who suffer much from bilious attacks, or what the poor call "the bile," which may, I think, be translated as gastric dyspepsia with consequent uric-acidæmia, often derive great benefit from leaving off their meat, wine and beer and, in fact, reducing their nitrogen; and, if I am correct in my inferences, it is the uric-acidæmia thus brought about that is the active occasioning cause, in other patients with more sensitive or irritable nervous systems, of headache, epileptic fits or mental depression, and the cure of one condition is the cure of the other.

And, thanks to the kindness of my friend Dr. Tooth, I have been able on numerous occasions to watch his out-patients at Queen Square, and have seen quite enough to convince me that in a very large number of cases the fits of epilepsy bear precisely the same relation to gastro-intestinal dyspepsia and the uric-acidæmia it produces as do headache and mental depression; and, on careful inquiry, it was surprising the number of cases in which the fits were apparently related to the causes which, in those not subject to epilepsy, would produce dyspepsia and a bilious attack.

If there is any warning of the approach of an attack, a dose of a nitrite, an acid, or of morphine subcute may be given. In fits it is necessary to act so quickly that our choice of drugs is more limited than in the case of headache; but I have met with quite a number of cases in which the patients have

asserted in a manner that it was hard to disbelieve that one or other of these things had prevented the fits, or reduced their number, or relieved the heaviness and stupor following them, and in several cases the patients have made signs for their dose of acid as soon as they recovered consciousness, as they found that it shortened the period of drowsiness, and headache.

In epilepsy, just as in headache, if there is much gastric disturbance this must be attended to in the first place, and drugs given only subcute or per rectum meanwhile.

Mental depression is almost the exact parallel of these other troubles, and what improves the one will improve the other.

When it is accompanied by slow high tension pulse and scanty urine, anything that relaxes the arterioles, quickens the pulse and increases the urine, will also improve the mental condition probably because it has the same action on the circulation in the brain as it has on that in the kidney.

Acids, opium, mercury, wine, beer, cocain, all have this action, and it is mental depression or a kindred condition produced by uric-acidæmia which has, to my mind, been in a very large number of cases the occasioning cause of excessive indulgence in some of these drugs or beverages.

Mental depression bears just the same relation to dyspepsia and its causes that high tension pulse, headache and epilepsy do. Perhaps the most interesting cause, because it is one very frequently met with and which has a very markedly similar effect in all four conditions, is menstruation, and it has this effect because it produces dyspepsia and failure of metabolism with uric-acidæmia (see pp. 79 and 135-6.).

The treatment, therefore, of mental depression, when not due to organic disease, is the treatment and prevention of uric-acidæmia.

Obviously, also, if uric-acidæmia affects the circulation in other organs and tissues, in the same way functional derangements of many other organs may be similarly treated.

The treatment of gout must vary considerably with the stage at which it has arrived ; but the main indications are perfectly

clear, as I have said—namely, to clear all the urate out of the body and to diminish its formation for the future.

How far this can be done in individual cases must depend on many points which it is impossible to go into minutely, and I have previously mentioned the way in which urates may be first cleared out, and then the whole nitrogen metabolism gradually reduced to a lower level.

As regards the acute attack of gout, anything that promotes the free excretion of urates will do good—as salicylates, alkalies, colchicum (which acts as an alkali and diminishes the acidity of the urine); while things that prevent its free excretion and promote its retention in the body generally, and the affected joint in particular, will do harm—as iron, lead, zinc, calcicum, opium, acids (including wines and beers, cider, etc.), mercury, antipyrin, nitrites, sulphates, hyposulphites and other salts of the mineral acids.

Among solvents I should give the palm to the salicylates, but they will act best in sthenic cases where acidity is high, or where some fever raises the acidity, for reasons I have previously given. The chief point is not to give less than gr. xv. four times a day, and to push it if necessary to six or eight times a day, and not to give alkalies with them, but rather sp. am. aromat., a little morphine, or something that raises the acidity; and as regards diet, especially in slight non-febrile cases, do not cut off meat and wine while you are giving salicylates; they will act as acids and aid the action of the drug.

Of rheumatism, much the same might be said; indeed, it must be evident that I regard gout and rheumatism as variations of the same disease rather than different diseases, and all that I have said about solvents applies to the one as much as the other.

In acute rheumatism a salicylate is, just as in gout, the best solvent, and as very important organs and tissues may be in danger the indication is to get the patient fully under its influence as quickly as possible—as there is fever the acidity is generally high enough; but do not give the drug with alkalies

or anything that will lower the acidity. I like to give gr. xv.—xx. of the soda salt every two hours till two drachms has been taken, and then enough to keep up the effects; and where I am not obliged to reduce the dose, I prefer to give 60 to 90 grs. in the twenty-four hours for seven to ten days after the temperature is normal. While this dose is continued it is not necessary to be nearly so careful about diet, and the patient may be put on ordinary diet minus meat and beer (and I believe that even these last-mentioned articles might be taken with impunity) almost as soon as the temperature is normal, if salicylates are kept on.

I cannot agree with those who having given, what I should regard as a totally insufficient dose of salicylate, discard it as of no use, and rush "out of the frying pan into the fire," to use opium, antipyrin, and other drugs, which must raise the acidity and do harm; and the unfortunate results recorded in some cases so treated, are pretty much what I should expect (see *B. M. Jour.*, vol. i., 1891, p. 1068, and *Practitioner*, May, 1891, p. 326).

In chronic rheumatism and rheumatoid lesions, the indications are much the same as for chronic gout; first clear out the urate and prevent its return by diet, and then treat the lesions of structure it has produced, and kept smouldering on.

In a very considerable number of cases that are clinically rheumatoid arthritis, salicylates have given very considerable relief, quite as much as any other drug that I know of; they seem likely to do good when the disease blazes up for a time into fresh activity, especially if there is any temperature. Where it is very chronic, and especially in hot weather, where there is much perspiration, and consequent loss of acids from the skin, the acidity of the urine may be low, and the alkalinity of the blood considerable; under these conditions the good effects of salicylates may be increased by giving them in alternate doses with acids.

If salicyclates, which did good at first, gradually fail to cause improvement, it is probably best to leave them off,

and to give up the treatment of urates; one may then devote oneself to the treatment of the lesions of structure they have produced, by alteratives, such as cod liver oil, or iodides internally, and measures directed to the improvement of digestion and general nutrition, and locally, blisters, massage, and electricity, as recommended and carried out successfully by Dr. Eccles. If, at any time, there is again a blaze-up, treatment of the urate factor should again be resorted to.

Diet also has often a most important influence, in more ways than one, both on the urate and the nutrition of the injured structures. A case from my own experience will illustrate some of these points.

A lady, of some sixty odd summers, a connection of my own, and one of whose sisters has had well-marked gout, suffered from great pain and stiffness in the joints of the lower limbs, especially in the knees, and in these there were well-marked rheumatoid changes: the result was that she could only get down stairs slowly, and with great difficulty. She paid one or two visits to Buxton, and did other things without much benefit.

When my attention was directed to her case, I noticed that she seemed to be decidedly worse at the end of July, throughout August, and the beginning of September, and after that she improved again somewhat. At first, I could see nothing to account for it, and was inclined to put it down to damp, which was her own idea, but then she ought to have got worse instead of better, later in the autumn.

I then began to observe her diet, and found that she ate a very large amount of soft food, porridge, sop, soaked bread, puddings, &c., and drank a considerable quantity of tea, and took but little solid, dry food; she ate some animal food three times a day; but always preceded or followed by an excess of soft food. Further, during the summer and autumn months, in which her pains were at their worst, she added to all this a large, I might say, a very large quantity of

the fruits in season. On further enquiry, it also came out that her bowels were nearly always relaxed to the extent of two or three loose motions in the twenty-four hours, and that this also was most marked in the fruit season.

I began to think I could understand, at least part of the cause of her trouble. I persuaded her to let me alter her diet. I replaced a large part of the sloppy food by toast and butter, and gave egg, fish, and simple roast meat in place of more elaborate dishes with sauces; and got her, as far as possible, to drink after her meals instead of with them, and most important of all, I allowed her but very little fruit. The effect was wonderful, and exceeded my utmost expectations; the pains and stiffness cleared up like magic, and she was soon able to run downstairs comparatively nimbly; and she lost, to a considerable extent also, the looseness of the bowels, and other signs of dyspepsia. She was greatly impressed with the result, and kept to my directions as to diet, for several years, and while she did so, her joints remained much better.

Now, what was the explanation of all these facts? I do not know that I can answer that question; but the hypothesis on which I worked was somewhat as follows:

Intestinal dyspepsia, with excessive fermentation, causing diarrhœa, favoured by a large consumption of sloppy food, and an excess of fruit; as a result of the fermentation, the production of certain bodies in excess, possibly, according to Bouchard acids, which would tend to precipitate urates upon her damaged joints, and keep going the rheumatoid processes.

But my critics will say now, here was a case of chronic rheumatoid arthritis in which, as you tell us, you gave great relief by knocking off farinaceous food and fruit, and yet you are going, we suppose, to advise the use of farinaceous diet and fruit in the treatment of similar cases?

But this patient, it must be remembered, was not only taking the fruit and farinaceous food which I do advise, but she conjoined with them a considerable amount of animal

nitrogenous food which I do not advise; and it was the mixture which did the harm. My impression is, that if she had first cleared her body of urates and reduced her nitrogenous income, she might have taken the farinaceous food and fruit without injury.

I think that the admixture of food not only promoted the dyspepsia and fermentation processes, but the resulting acids had plenty of urate on which to act because the nitrogenous metabolism had not been reduced. My own experience is that I can take butter and fat and fruit to almost any extent, so long as I abstain from nitrogen from animal sources; but if I add on to them an ordinary ration of meat, I very soon get gastro-intestinal dyspepsia and a "bilious attack," and at the other end of the cycle arthritic pains. In the above case I think it is quite possible that the acids produced by fermentation were more important than the rise of acidity which must have been produced by my alterations in the diet; the leaving off of a certain amount of farinaceous food and all the fruit must have reduced the income of alkali, but a more important formation of acids which had been going on practically ceased.

Some facts running parallel to those above mentioned are, I think, to be seen in the relative frequency of gout in England and Germany.

The English, I believe, eat more meat than any other nation in Europe (see *Lancet*, vol. ii., 1890, p. 409, and prev. ref. in Chap. VIII.); they drink a good deal of acid beer and suffer in consequence from retention and accumulation of urates (gout); but the Germans consume a large amount of beer, and yet do not, I believe, suffer from gout to anything like the extent that the English do. The explanation is probably quite simple—namely, that the Germans eat less meat than the English, and therefore form less urate, and though their acidity is doubtless kept up by the beer they drink, their urate accumulations are less than those of the English, because there is less urate for the beer to act upon; but their acidity also is less, as the salts of meat tend to raise acidity.

We thus see that if the formation of urate has been reduced, acids, wines, and beer can be taken with comparative impunity because there is very little for them to act upon. It is not, therefore, by any means necessary to enforce and maintain a rigid abstinence from alcohol, wine and beer; alcohol alone, as we have seen in the case of the Scotch, has little or no effect in producing gout, and wine, beer, cider, etc., only do harm from the acids they contain acting on the urates they meet with in the body; but once the excess of urates has been cleared out, and their formation reduced, there is nothing to prevent the moderate use of wine, beer or, indeed, of any acid drinks, when there are other indications for them, such as debility or morbus cordis; they can no longer do any harm in precipitating an attack of gout, or accumulating urate to any serious extent within the body.

In the chapters on gout and rheumatism I have said a good deal about the circulation in, and the nutrition of joint structures in the old and young, and it seems to me that the effects of electricity, massage, warmth, and of a warm dry climate may be very considerable in this direction, in that they may all tend to improve the circulation in peripheral joints and thus to bring their alkalinity more into harmony with that of the blood and other portions of the body, so that they cease to be the least alkaline portions of the body in which urates tend to become insoluble.

Obviously, however, if the urate in the body is reduced and kept low, these structures will suffer less, even if their alkalinity is reduced; but the very process by which the urate is kept low—namely, reduction of nitrogen, and especially of animal nitrogen, and a liberal supply of vegetable products and fruit, tends to increase the alkalinity of all the tissues and fluids of the body; hence the treatment I suggest affords the most absolute safety against arthritis, in so far as it is due to urates, and by the application of these principles we shall eventually see how far that is.

In the case of children of markedly gouty and rheumatic

families, or of those in whose family bilious attacks, headaches, or epilepsy are prominent, I consider that a decided reduction of the animal nitrogen in their food is strongly indicated as a prophylactic measure; and I think that many lives may be saved and much misery from chronic morbus cordis may be averted by such measures.

I have pointed out (p. 172.) what M. Bouchard says of the deadly effects of a highly animalised diet in children in precipitating those diseases, and it follows from this and my previous reasoning that an early and continuous reduction of animal food may be a most important recommendation in such cases, and indeed, I believe that there are few children who would not benefit by it.

What M. Bouchard speaks of as "ralentissement de la nutrition" is doubtless, in these cases, the diminished metabolism which uric-acidæmia produces in the muscles, liver and other organs by interfering with their circulation (see p. 123), as we have seen that it does in the case of the kidneys (p. 100).

Further, if my reasoning is correct, such a reduction of animal nitrogen entailing a diminished formation with increased excretion of urate, thus lessening in two ways the amount contained in the body, would, if effected early in life, rob many of the acute febrile diseases from which children so often suffer of some of their most deadly complications and sequelæ—such, for instance, as morbus cordis, and Bright's disease.

With regard to glycosuria and diabetes, I have little or nothing to add to what I have already said in quoting my cases. The points I specially bear in mind are to give salicylates to the extent of at least gr. 60 in twenty-four hours for an adult, and if the total acidity of the day's urine is low, to give acids or some drug which will raise the acidity—as opium, morphine, or sp. ammon. aromat. along with them. As a rule, I think it is well not to alter the diet before or during the administration of salicylates, and not to give them while there is any gastric disturbance or any temporary cause interfering

with digestion. When the salicylates have been taken for some time and are well in action and keeping the sugar low, the amount of animal food may be reduced towards that of ordinary diet, and in some of my cases I was able to allow ordinary diet with the exception of potatoes without increasing the sugar excreted and with benefit in other ways. For, if my reasoning as to causation is anywhere near the truth, the excess of animal food generally given, though it for a time raises acidity and clears the blood of urate, and so does good at first, yet, as it must increase the nitrogenous metabolism and the formation of urates, it tends to increase the congestion of the liver and to further hamper the metabolic processes in the skin, muscles, etc., which may be the central factors in the causation of the glycæmia.

Further, this large nitrogenous metabolism must lay up in the body a store of effete products (urates and others) which, from my experience of the effects of urate on the nutrition and function of many important structures and organs, I should be very sorry to carry about in my own body; so that I regard it as the most important advantage of the salicylate treatment that it eliminates quickly and safely this excess of urates, and further allows the patient in some cases to return towards a less highly nitrogenised and more natural diet.

In Bright's disease, again, the indications are very simple: (1) to remove the poison (urate) from the blood; (2) to diminish the amount of albumen that has to be metabolised, and to give such quantity as is necessary in the form of milk which, according to Semmola, is most easily assimilated; (3) to use all means, such as hot-air baths, friction, blankets and warm clothing, to promote the functional activity of the skin.

Urate may be cleared out of the blood by the use of acids, opium, or other drugs which interfere with its solubility; but we must remember that these do not bring about its elimination from the body, and that they are useful for a time only, and for such temporary purpose as clearing the blood of urate at some sudden and dangerous crisis.

As regards opium, I have used it only in a few sub-acute cases in small doses and with careful watching; but in these cases it has reduced the tension, quickened the pulse, increased the urine, and diminished the albumen.

I have more often made use of acids, and in some cases have given salicylates in alternate doses with them, thus bringing about the elimination of the urate from the body; this also produces more effect on the pulse than acids alone (see fig. 20) and has certainly not increased the albumen; but my experience with it is not sufficient to enable me to say that it may not do so in some cases.

With regard to opium and morphine, we must remember that their use has been advocated in uræmia and in uræmic and puerperal convulsions (see *Brit. Med. Journ.*, vol. i., 1889, p. 588, 837 and 943), and this being so, it is quite possible that they may be of use in other stages of Bright's disease quite apart from any theory about their action.

Then, again, alkalies may be used to effect the removal of urates from the body, and it is probable that they may be of considerable use in acute cases, by increasing the alkalinity of the kidney which we are supposing to have been reduced by the local inflammation.

For if, as I have suggested, the chronic uric-acidæmia of Bright's disease is due to a block in the elimination of urate owing to the diminished alkalinity of the kidney, alkalies given to the extent of increasing the alkalinity of the kidney must facilitate excretion and do good. To obtain this effect it is probably necessary to give them in considerable doses so as to render the urine quickly alkaline and keep it so; their first effect will no doubt be to increase the uric-acidæmia, but if they overcome the block in the kidney a considerable amount will soon be eliminated, and the amount in the blood will be correspondingly diminished.

When uræmia is due to the effects of high arterial tension on the nerve centres, and the high tension is due to uric acid, it will react in the way I have already spoken of to drugs that

affect uric acid—such as acids, opium, nitrites, etc., with or without the addition of salicylates; and I cannot but regard it as pretty strong proof that uræmia is in many cases merely uric-acidæmia, that the symptoms of the one condition should so greatly resemble those of the other, and that the effects of drugs should be so very similar in each.

The treatment of the abuse of drugs such as morphine, cocaine, alcohol, is the treatment of uric-acidæma, with considerable accumulations in the body; first, remove the accumulations, then gradually reduce the dose of the drug, using in its place, to a certain extent, other drugs that clear the blood of uric acid (see p. 33), and when the drug has been completely left off, provide against any recurrence of severe uric-acidæmia, by permanently reducing the nitrogen, this latter precaution having been found, as I have mentioned, of considerable value in the case of alcohol.

Practically then, all these diseases will be benefited or prevented by eliminating urates from the body, and then permanently reducing their formation, and I shall now go into the method of effecting this by means of diet.

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 uric-acidæmia, 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 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; and animal food should be steadily reduced till the urea has been brought down to the required extent, say to three-fifths or one-half of its quantity on ordinary meat diet.

On ordinary diet, including a fair quantity of meat once or twice a day, my urea used to be between 500 and 600 grs. in twenty-four hours; and I shall now give an outline of the diet which has reduced it to about 300 grs., giving me, at the same time, immunity from uric-acidæmia, and its unpleasant results; and I think it will be seen that there is not much in it to frighten anyone, and that there is absolutely no danger of starvation.

The totals are roughly :—

ANIMAL FOOD—

Milk, 1 to 1½ pints (previously boiled).

Egg, Fish, Fowl, or Game, 1 to 4 ozs., varied a little from day to day.

VEGETABLE FOOD—

Vegetable prepared products
Vegetables twice a day
Fruit three times a day
} to any desired extent according to appetite.

Tea, Coffee, Cocoa } In moderation, and as flavourings rather than as strong decoctions.

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.

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, as in the case I narrated above, 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, 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 300 grs. a day.

Breakfast.—A large soup plate, half full of porridge, eaten with milk. (I prefer it made with salt).

A few mouthfuls of fish or egg, prepared in various ways.

One to two rounds of bread, or its equivalent in toast or scones, with plenty of butter.

A cup of milk, flavoured with tea, coffee, or cocoa (previously boiled).

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.

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, of which only a very small bit is taken.

Two vegetables, with sauces, butter, or fat.

Any ordinary pudding, tart, or stewed fruit; though not as a rule very rich dishes, containing many eggs.

Biscuit and butter.

A good supply of various fruits for dessert.

For drink, water with syrup, ærated waters, or a little milk, which I often take warm in winter.

A tumbler of water, ærated water, or in winter, hot water, at bedtime.

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 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; 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, etc., 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.

INDEX.