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Uric Acid.

its

Etiology

Physiology.

Pathology.

and Treatment. as far as

is suggested by the previous enquiry.

by.

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There are few subjects of study with which the Physician can more profitably employ himself than that of the manifestations of Uric Acid in the Human Body. not only in its classical and typical forms of Gout and Gravel. but also in those Proteau forms included under the general and somewhat indefinite term Gouttiness.

In the former case no great acumen is required to diagnose and treat the condition, but in the latter only the trained eye and educated judgement and the Capacity born of much experience and a full knowledge of the various ways in which the peccant material is generated, and the conditions under which it manifests its presence. can successfully recognize and treat the Complaint. When we remember too that by its presence in the blood and tissues in abnormal quantity many lives are one long misery from the cradle to the grave. and that a true physiology and pathology can only be founded on a strictly accurate Chemistry. we can find no higher sanction for a complete and exhausting study of its Aetiology. Physiology Chemistry and Pathology. for only upon such knowledge Can clear rational and definite principles of prophyllaxis and treatment be founded.

Did Uric Acid always manifest its presence openly and unequivocally. as in Gout and Gravel. the problems the physician is called upon to solve in its detection and treatment would be Comparatively

simple. But when we remember that Uric Acid is a normal product of metabolism. becomes pathological whenever it is produced in excess. or fails to be excreted with sufficient rapidity, and that the limits between production and excretion are extremely narrow. its presence in the body assumes a position of greater importance

Though it manifests itself chiefly in two forms. viz. as Gout and Gravel. and tho' the injurious material in both Conditions is the same. yet the two Complaints are not substantially one and the same as has been pointed out by Sir W Roberts (Croonian Lectures 1892 p56). He says that many gouty people. are never troubled with gravel and conversely. In both there is an aberration of Uric Acid, but the error is essentially different. in the two Cases. both as to site and to nature In Gout the error occurs on this side of the Kidneys. in the blood and tissues. and the Uric Acid is precipitated in a state of Combination as Sod Urate. In Gravel the error occurs on that side of the Kidneys. and the Uric acid is precipitated in the urine, and in the free state. In the former the deposition takes place in the true interior of the economy. in the latter the deposit occurs. in what is strictly-speaking. ~~the true interior of the economy. in the latter the deposit occurs. in what~~ is ~~strictly speaking~~ the exterior of the economy ie on

" the surface of a doubling of the external integument".

Moreover in the the former case the deposit takes place from a fluid and vital organ - the blood. with high capacities for self-adjustment to a normal standard, as regards. quantity, quality and reaction. where Life of whose nature we are ignorant, and whose laws we are only laboriously spelling out, manipulates the molecules and atoms.. and plays with a Chemistry of which we are sublimely ignorant... while in the latter the deposit takes place in a dead excretion without power of self-purification. but whose Chemistry we can both study and imitate.

Nor is its presence seen only in these two conditions, since it exists in solution in the blood. which bathes all tissues, there is no system free from the manifestation of its presence. when once it exists in abnormal quantity. Frequently when pathological conditions are present in any system. a gouty or uratic colouring is given to the disease. hence the use of such terms as Gouty Phlebitis Suppressed or Retrocedent Gout. Visceral Gout. . Gouty Neuritis and Paralysis. Gouty Skin disease, Gouty Disease of the Throat. (Sir Morell Mackenzie). Gouty Asthma and Bronchitis &c. their connection with Uric Acid being shown by the fact. that they disappear upon the supervention of a classical and typical attack. of Podagra or Chiragra.

In such Cases it is of the utmost importance to

be able to recognize. the underlying "Diathesis" (a faculty much praised and enjoined upon his students by the late Prof Laycock.) for our treatment will be in vain till that is recognised and allowed for.

Before proceeding to the complete study of the Etiology of Uric Acid. and the laws of its Chemistry both in the blood and urine. it will be advis-able to glance. shortly at some of the theories. which have been advanced. by men eminent in the profession. who with ample material at their Command. yet with a more restricted knowledge of Chemistry and of the experimental data. at our command. during the past few years. endeavoured to explain the phenomena. exhibited in the Aberrations of Uric acid by the light of such knowledge as they had. Many. of these theories though crude. when viewed from the stand-point of today. Contain instalments of the desired solution or hints in the right direction

In glancing backwards. to the days before the study of medicine was subjected to experimental methods. we find the two great schools of pathology. the Humoral and the Solidist. but from our point of view. these two Conceptions are as inseparable as the fluids and solids of the body are. Stated Crudely the Humoral Theory runs thus. "the fluids found in the alimentary Canal, in the vascular System, in the secreting and excreting glands

and in the tissues themselves are the agents of disease.".

Sydenham

The last of the great apostles of the "Humoral" theory was Sydenham who adhered to the view that in Gout. "the blood is vitiated through the defect or disturbance of the secretions especially the Hepatic and Digestive secretions.

Cullen

Then Cullen attributed the production of Gout to abnormal function of the Nervous System.

Scheele 1775
Wollaston 1797

In 1775. Scheele discovered Uric Acid in Calculi and in urine. The next step was taken by Wollaston who modified the humoral theory by discovering the presence of Uric Acid in Gouty Concretions: but it was reserved for Garrod to point out the connection between Uric Acid and Gout. by demonstrating the presence of Uric Acid in the blood and tissues of the Gouty. by his well known thread experiment. which today is demonstrated to and repeated by every Tyro in Medicine at all the schools.

Garrod 1848

Mechanical Theory

He then showed that Uric Acid caused damage not while in solution in the blood. but when deposited as Bi Urate in and about the Joints

Toxic Theory

Latin. Dr Haig while not denying the above maintained that Uric Acid manifests its deleterious action while in solution and circulating in the blood

Mechanical-Toxic

Then Ebstein combines these views. and conceives a double and reciprocal influence Toxic on the one hand and Mechanical on the other. between the tissues and the Uric Acid.

Nervous Theory. Later Sir Byrce Bickmorth propounded a Nervous Theory. But better than a historical classification is the following one. for which I am indebted to Ewart in his book. published (Dec 1896) after this paper existed in small form. and which I have adopted as superior to my own. (Ewart p 31).

(1) Chemical. (2) Modified Chemical. (3) Histogenous (4) Nervous.

(1) Chemical Theories.

A. Garrod's Theory of Uric Acid excess and Renal Inadequacy.

(Practically in all the following Theories Uric acid is regarded as the peccant materies morbi. but different views are held as to the mode of its action. The following part of the paper is an attempt to reduce the whole question of the existence and action of Uric acid in the Human body to the arbitrament of the experimental method. and to show how this has been done partially by some workers and partly by others)

Garrods Theory.

The phenomena of Gout are dependant on the pre-existence of Uric Acid in the blood. - and their local manifestations are due to its deposition as crystalline Sodium Biurate in the tissues.

The first step in the pathological process is faulty action (functional) on the part of the Kidneys. which may be inherited or acquired. by which they show reduced efficiency in clearing the blood of Uric Acid. The function of the Kidneys is not to form but to excrete.

Uric Acid and Urea. The imperfection in the eliminating power of the Kidneys sometimes appears to be the chief, if not the only cause, of the impurity of the blood. (Garrod. A Treatise on Gout p 280). He sums up his Conclusions as follows. (Loc. cit. 3rd Ed. pp 274-5).

1. In true Gout Uric Acid in the form of Urate of Soda, is invariably present, in abnormal quantities, both prior to and at the period of the seizure, and is essential to its production, but this acid may occasionally exist - at least for a time, in the circulating fluid, without the development of inflammatory symptoms, as in cases of Lead Poisoning. Its mere presence therefore does not explain the occurrence of the Gouty paroxysm.
2. The investigations detailed in the chapter on Morbid Anatomy of Gout prove incontestably that the truly Gouty inflammation is always accompanied by a deposition of Urate of Soda in the inflamed part.
3. The deposit is crystalline and interstitial, and when once the Cartilaginous and ligamentous structures become infiltrated remains for a lengthened time, often throughout life.
4. The deposited urate of Soda may be looked upon as the Cause and not the effect of the gouty inflammation.
5. The inflammation which occurs in the gouty paroxysm leads to the destruction of the Urate of Soda in the blood of the inflamed part, and Consequently of the system generally.
6. The Kidneys are implicated in Gout, probably in its early and certainly in its Chronic Stages. And the renal affection, possibly only functional at first, subsequently becomes structural. The urinary secretion also becomes altered in Composition

7 The impure state of the blood. arising principally from the presence of urate of Soda. is the probable cause of the disturbance which precedes the gouty seizure. and of many of the anomalous symptoms to which sufferers from Gout are liable.

8. The causes which predispose to Gout independantly of those connected with individual peculiarity. are either such as produce an increased formation of Uric Acid in the system, or lead to its retention in the blood.

9. The causes exciting a gouty fit are those which induce a less alkaline condition of the blood. or which greatly augment for the time, the formation of Uric Acid., or such as temporarily check the eliminating power of the Kidneys.

10 In no disease but true Gout is there a deposit of Urate of Soda in the inflamed tissues."

B **Pfeiffers Theory.**

The gouty attack due to a resolution of deposits.

He assumes that in the Uric Acid Diathesis Uric Acid takes on a less soluble form and is therefore less freely excreted. and therefore is gradually deposited in the tissues. No change will happen so long as the tissues maintain their alkalinity. but should a wave of increased alkalinity pass over the blood. the deposits are re-dissolved and act as a chemical poison. and this is evidenced by the pain and pyrexia of a gouty attack. He finds support for this theory in the clinical

observation that. " in gouty conditions pain is increased after the administration of alkalies - while it is relieved by acids especially Salicylic Acid in large doses" The objection to this Theory is found in Sir W Roberts experiments - by which he showed that it is exchimely difficult to make much impression on the reaction of the blood. by exhibiting Acids or alkalies - as they are quickly excreted by the Kidneys. Freddeberg (Virchows. Archiv. B° 125 p 566) and others have confirmed this fact experimentally

C Ebstein's Theory.

The destructive action of Urates on the tissues

According to Ebstein. (Beiträge zur Lehre von der Harnsauren Diathese 1890 p 23). Gout depends upon an abnormal extension of the sources of the supply of Uric Acid. It is found in abnormal situations eg Bone-marrow. Cartilage Muscle. Take on its manufacture. or it may be produced in these tissues. in abnormal amount. The proportion of Uric Acid. circulating in the lymph and blood. being thus increased - when from any accidental cause. Stasis occurs in the lymph-vessels. in any part - and the concentrated solution of the urates. contained in the stagnant lymph-stream has time to act. Necrobiotic changes are set up. and as a result the tissues change their alkaline reaction to an ~~alkaline~~ acid one. - at that moment a precipitation of Sodium Biurate takes place. and an attack of Gout begins. When such a deposit is afterwards dissolved off. a necrotic surface is.

invariably exposed. and Cohnheim finds in this the Confirmation of his theory.

jections (1) That Uric Acid is formed in various tissues not usually Concerned with its formation. is disproved by Horbaczewski's proof that in health Uric Acid is a bye-product of the metabolism of almost all tissues. (memorandum posted)

(2) When demonstrating the formation of necrobiotic patches in the Liver and Heart-wall by ligaturing the ureters of Birds and Serpents. he was not imitating a physiological process. or even a pathological one. but reproducing the Conditions of Uraemia. and no condition similar to Gout

2. Modified Chemical Theories.

Theories of Hepatic Inadequacy (Murchison & Latham).

metional derangements of the Liver 2nd bet by Murchison 1879).

A Murchison showed that in addition to the secretion of Bile and the formation of Glycogen. one of the chief functions of the Liver. was the destruction of albuminous matter. derived from the food and tissues. and the formation of Urea and Uric Acid. which are eliminated by the Kidneys. and that deposits of Uric Acid and urates. and an imperfect formation of Urea. are frequent signs of functional. as well as of structural derangements of the Liver. At the same time he admitted renal inadequacy and as a consequence accumulation of Uric acid. in the blood. were associated factors in the production of Gout.

B Dr Latham's views. (On the formation of Uric Acid in animals and its relation to Gout and Gravel 1884).

According to this view. the imperfect metabolism of Glycocine. is the primary and essential defect in the formation of Uric Acid. and that therefore functional derangement of the Liver. is considered to take a prominent share. in the causation of these conditions. As in Diabetis there is an inability. to effect the metabolism of Glucose which then passes into the circulation. so in Gout and Gravel. the imperfect metabolism of Glycocine is the "fons et origo mali" In his Croonian Lecture for 1886. he says. of the Glycocine if it fails to be absorbed. " unchanged. it passes from the alimentary Canal. or elsewhere into the Liver. there under the action of the gland. it is conjugated with Urea. resulting from the metabolism of the other Amido-bodies. Leucine &c. and is converted into Hydantoins. It then passes on to the Kidneys. to be Combined with other molecules of Urea. or Biuret. forming Ammonium Urate. a portion of which overflows into the circulation. and is converted into Sodium Urate. If the Liver should become sluggish. as is likely to happen with Patients who take too much food. and too little exercise. or if the terminations of the Nerves. should. from excessive stimulus become somewhat paralysed. and the gland in some measure. like the sub-maxillary after the injection of atropine. - the result would be imperfect performance of functions and the non-metabolism of Glycocine.

The objection to this Theory is. - the assumption that

Uric acid is formed in the Kidney.

He invokes also the aid of the Central Nervous System without specifying definitely the locality of the suspected change. There is not a single word of experimental proof.

C

Dr Haig's Theory. (Uric acid in Causation of Disease Haig 3rd Edi 1896)

Uric Acid in the blood acts directly or thro' the Vaso-motor centre on the muscular fibre of Arterioles Capillaries causing increased pulse-tension and blood pressure and therefore Migraine Epilepsy Gout &c

This Theory stands alone in originality and in the unhesitating boldness with which it is stated. He cares not to enquire what preceded Uric Acid. He accepts Garrod's Theory of its formation and you are not too fastidious about the stability of this mid-air foundation everything is evolved smoothly on the lines of the Theory.

His book (op cit) is charmingly written and stimulating to read because one must stop so frequently to compare his physiology and pathology. But Dr Haig is seldom caught napping.

I give his Theory at considerable length because it is based to so great an extent upon the experimental method.

Now His Theory is based largely upon numberless experiments upon himself for which few men would have so much courage

From his youth he suffered from Headache. He tried drugs in vain. Then he tried change of diet to a meat only milk and fish. Then his Headaches fell from one a week to one per month, then one

every 3 months. Then every 6 - 8 - 12 months.
and eventually one in 18 months. but it returns
if a return is made to meat diet. Then he began
to seek for an explanation of these phenomena. and
found that Migraine had a very strong relation to Gout.
and therefore began to suspect Uric Acid might
turn out to be the cause of his trouble.

He then began to estimate his excretion of Uric
Acid and Urea. and found a definite relation between
the Headache and the excretion of Uric Acid.
He found that Dr Liveing in his work on Migraine had
described Concomitant symptoms. eg. slow high tension
pulse. Cold surface and extremities, mental depression
disinclination for exercise. the urine passed during
the Headache. scanty. high coloured and of high
specific gravity. He noted also that these Concomitant
symptoms had the same relation to the excretion of
Uric Acid. He found that his excretion of Uric Acid
was always within his control. and that he could
alter it from day to day and hour to hour.
at pleasure. (Trainual Phys. vol viii). His next point
was that by altering the excretion of Uric acid he
could alter the symptoms related to it. eg. increased
excretion of Uric Acid produced by taking an alkali.
always caused the Concomitant symptoms. i.e.
Headache. Mental depression. Cold surface. and
extremities. Slow pulse. Scanty urine. - when the
plus excretion stopped. the symptoms stopped -
He thus gained (loc cit p 3). "not only" power to produce or

" remove Headache. but. I had also the power to relase
" or contract the arterioles and capillaries. to affect the
" tension of the pulse. the rate of the Hearts action, and
" thus to influence the circulation. in the Brain.
" Skin Kidneys and probably. the whole body."

He observed that whenever an acid was given to diminish the excretion of Uric Acid he always experienced. pricking and shooting pains. in his joints (generally those most used on the day in question). he therefore concluded. that the Uric Acid was held back in these joints and caused the pain. and that the Uric Acid which failed to appear in the Urine. must have gone somewhere. and (~~that~~ as it was most natural to suppose) into the joints He found that Garrod described similar pains. when Gouty Patients took beer or wine. - all which he found to be acid. and therefore. seeing his theory thus confirmed he considered it established He then says

General Laws. (Op. Cit p. 4)." Since then. 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"

He based the whole of his writings on the above

facts and observations. He reasoned on the pathology of Epilepsy, and found an exactly similar fluctuation in the excretion of Uric Acid. to those met with in Migraine. and he ~~has~~ thought he had by this means cleared up a clinical relationship. which had long been known and written about. - as well as many of the facts of the pathology. of Rheumatism. Rheumatoid Arthritis. Bright's Disease. Raynaud's disease. Haemoglobinuria. Anemia &c.

If it be granted that Uric Acid affects the arterioles. in the way and to the extent claimed. it must influence for good or evil. the function nutrition and structure of every organ and tissue of the body. from the skin to the most central fibres of the spinal-cord.

The most valuable point of his discovery a fact which neither Garrod nor Roberts knew. (op. cit p7) he considers to be the "fact. that the excretion of Uric " Acid can be made to vary at any time and in " any direction" and that this revealed to him. 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 Roberts has called the alkaline tide and the smallest excretion in the high acidity period of the night.

He acknowledges. his indebtedness to Dr Livings work. for a knowledge of the relationship

of Migraine to Gaut. also of Migraine to Epilepsy and of both to Gaut — and to Du Bois Raymond. for a suggestion of the relation of Epilepsy to Migraine.

He states his next discovery as follows. (op cit p 8).

" I found (1). that Uric Acid taken by the mouth. passes into
" the blood. and that if this fluid is kept in a condition
" to hold it in solution. it will remain in the blood
" till the Kidney has time. to pass the whole of it into
" the urine. so that if grs 12. taken by the mouth.
" some 10 or 11 grains can be obtained from the urine.
" within 3 or 4 days. after it has been swallowed. (Jour Phys vol IV p 167).
" (2). that in so far as the morbid processes. of which
" I shall speak in the following pages. are due to an
" excess of Uric acid. in the blood. they can be
" produced at pleasure. simply by taking that
" substance by the mouth. and thus any one
" who wishes to do so. can repeat my experiments
" and satisfy himself. as to their truth."

His second discovery he states as follows. (op cit p 10)

" That Uric Acid when present in excess in the blood
" affects its quality. in an important manner.
" producing the changes met with in Anemia.
" Leucocytosis and Haemoglobinuria. and other diseases
" and also Counteracting the effects of iron and
" preventing it. from building up the blood.
" and curing these diseases.

Formation and excretion of Uric Acid.

He noted that on a day on which he had a
severe Headache the excretion of Uric Acid was

16 grains for 24 hours. while on a subsequent day. with the same excretion of Uric Acid. there was no Headache Evidently there was some other factor. whose operation had not been reckoned with. He observed that on the day. with no Headache the relation of the excretion. of Uric Acid to Urea. was as 1 : 33. while on the day with the Headache the excretion of Uric Acid to Urea. was as 1 : 20. He accordingly set about investigating what. the normal relation. of Uric Acid to Urea was. As the result of labours extending over 10 years. he came to the conclusion the relation was. Uric Acid : Urea :: 1 : 33.

He keeps his Urea about the physiological level by eating Substances which contain sufficient nitrogen but which introduce into the body. little or no Uric Acid or what amounts to the same thing Xanthin bases.

As far as the Headache was due to Uric Acid it is due to a fluctuation in excretion. no alteration in formation having necessarily taken place. He quotes similar figures obtained by Messrs. Yvon and Berlioz. (Revue de med. Sept 1888). who found as the results of their experiments. the relation to be from 1 : 30 to 1 : 40. Dr Duckworth quotes Lecanus figures. viz 1 : 33. (Lancet 2 1888)

When the Uric Acid formed. in the body. or introduced in a day in food. is excreted there is no Headache because no excess. of Uric Acid ~~in the~~ in the blood. When more is excreted than formed the surplus comes from the parts of the body. (liver. spleen. lymphatic tissue). where it had previously

been stored. during times of plus formation. introduction or retention. Stored Uric Acid on its way to the Kidney would pass through the blood. and would be for some hours in excess. in the blood. and would give rise to Headache. and other signs of its presence.
One grain of Uric Acid held back daily for a year. would amount to nearly an ounce in a year.

It is impossible to reproduce all Dr Haigs diagrams. and in one respect that is much to be regretted. for they are not only exceedingly suggestive but one can scarcely understand his Theory without them. I shall however reproduce a few. which are absolutely necessary. to illustrate his meaning.

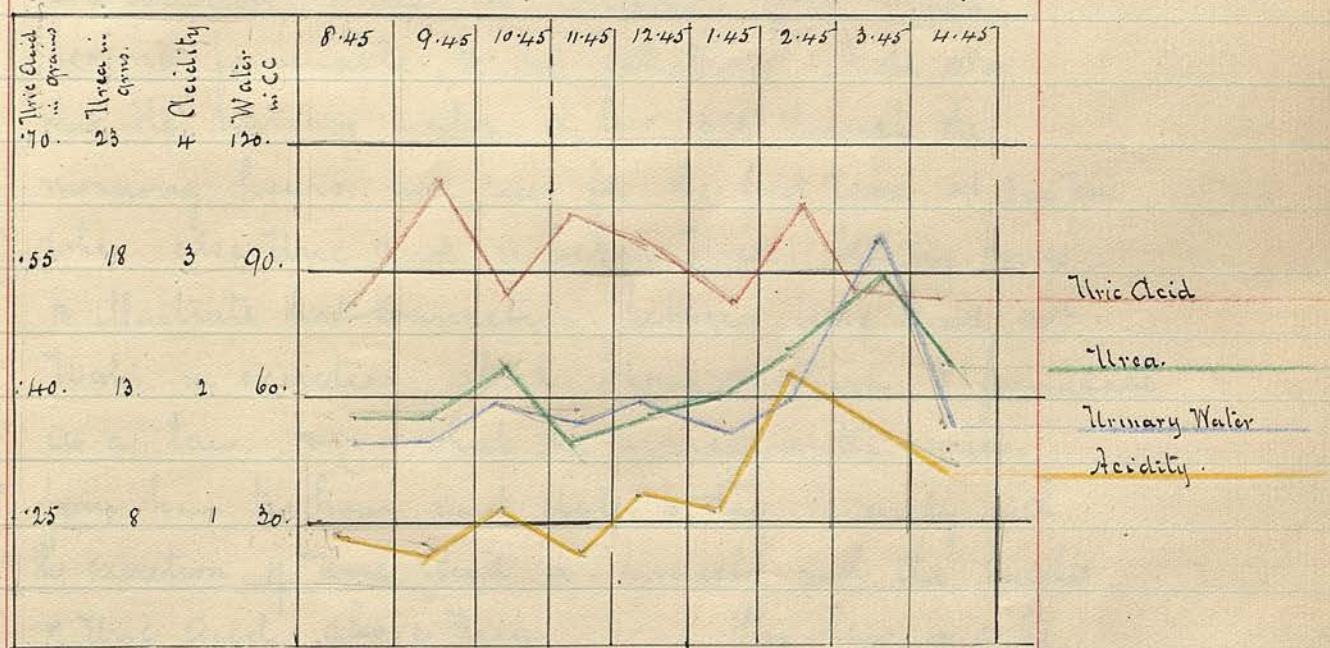
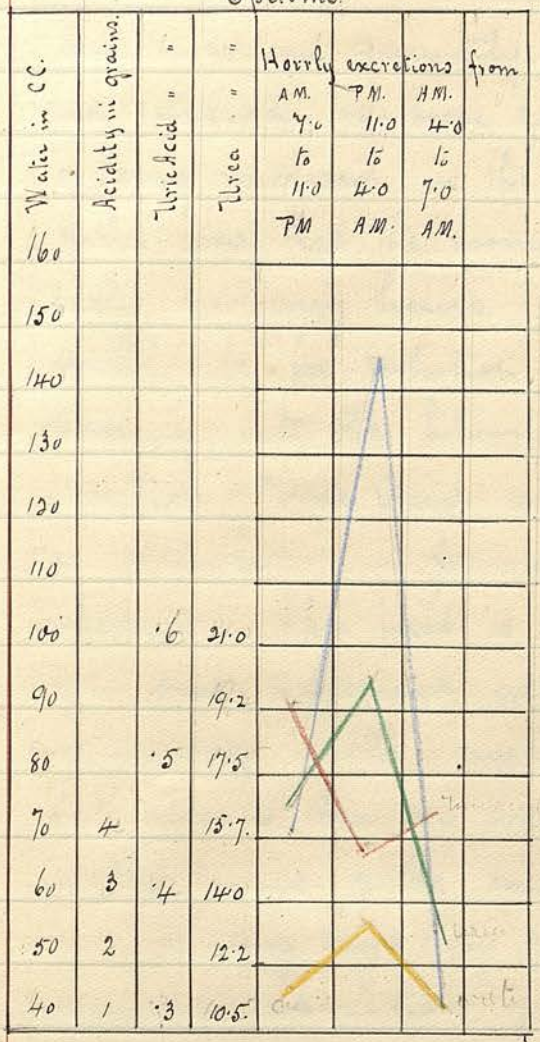


Fig. 1. (p 17). Shows the natural + excretion of Uric acid. which occurs in every one every day. The exact hours in which it will fall depends upon their habits as to food, exercise, sleep &c. because these control the daily fluctuation in acidity. and the acidity

" Controls the excretion of Uric Acid By altering
" Completely the acidity of the whole day. we can alter
" Completely the excretion of Uric Acid. also. throughout
" the whole day. As a result of this law. Acidity
" in the AM. and early PM hours. Uric Acid is above
" Urea (i.e. the normal relation 1:33. is interfered with
" and comes below it for the first time at 3.45 pm
" We must bear in mind however. that this high Uric
" Acid is dependant on 2 factors. (1) the law acidity
" of the urine corresponding to the high alkalicity of
" the blood. and rendering that fluid a good solvent.
" of Uric Acid. and (2). the presence somewhere in
" the body. of a quantity of Uric Acid available
" for solution. when the condition of the blood.
" becomes favourable. to this solution. Note also
" that the urinary water. is low all through the
" morning hours. and rises for the first time at 3.45 pm
" when also Uric acid is below Urea. This fig. serves.
" to illustrate that connection. between Uric Acid and
" Water in excretion. which I have ventured to formulate
Law. " as a law. viz. That the urinary water varies.
" from hour to hour and day. to day. inversely with
" the excretion of Uric Acid. or. inversely with the height
" of Uric Acid above Urea. ---- This law is of the
" utmost importance in enabling us to prove. the
" power of Uric Acid over the circulation of the whole body.

Figure 2. shows the excretion of Uric Acid
Urea Water and acidity in epitome. The curves
represent the average hourly excretion in each period

Fig 2. Daily excretion of Uric Acid in Epitome.



We see that in the hours 7 am to 11 pm (ie the usual working-day hours). Uric Acid is above Urea. and water is low. Acidity is also low. and this is the cause of the high Uric acid. In the hours. 11 pm to 4 Am. acidity and urea. have risen considerably. as a result of the high Acidity Uric Acid has fallen considerably below Urea. and as a result of this low Uric Acid. which means absence or relative absence of Uric Acid from the blood. The arterioles and Capillaries throughout the body. have been able to relase. and as a result of these relased vessels. in the Kidneys. there has been a free. elimination of water from the blood. and a diuresis " since. the urinary water. is as we see very high. " In the hours. 4 Am to 7 am. we see that Acidity falls " to its lowest point. . that urea falls very greatly. that " water comes down also to its lowest point. and " that Uric Acid rises. which is due to the fall of Acidity. " and also to the relation of Uric acid in the " previous night hours

When the Uric Acid was low in the night there was no alteration in its formation. relative to urea. it was being formed then as always. in the relation to it of about 1:35. but the Condition

of the blood. was unfavourable to its solubility and a certain quantity of it was being held back and retained in some of the organs and tissues instead of being excreted in the Urine. and the consequence of this was. that the moment the acidity fell in the early morning hours. there was some Uric Acid available for solution in the blood. and this passing into the blood and urine. raised the excretion of Uric Acid above Urea. there being again no alteration in formation (relative to Urea) whatever. This fact is easily demonstrable for if you give sufficient alKali to prevent the rise of acidity in the night hours. you will find that there is then no excess of Uric Acid passed in the urine of the early morning hours.

Dr Haig lays very great stress upon this figure and his exposition of it. He regards it as the key to all his work. He says regarding it.

You will find as a matter of experiment that by controlling the acidity or the Uric Acid and producing changes in these such as are shown in the figure. you are able to control to a large extent the Urea and to a still greater extent the urinary water. and that these are the signs and results of similar but more important control over the arteries and capillaries - the blood pressure the action of the Heart and the physiology of the whole body -

Acidity may be controlled by giving alKalies - by increase or diminution of activity and perspiration

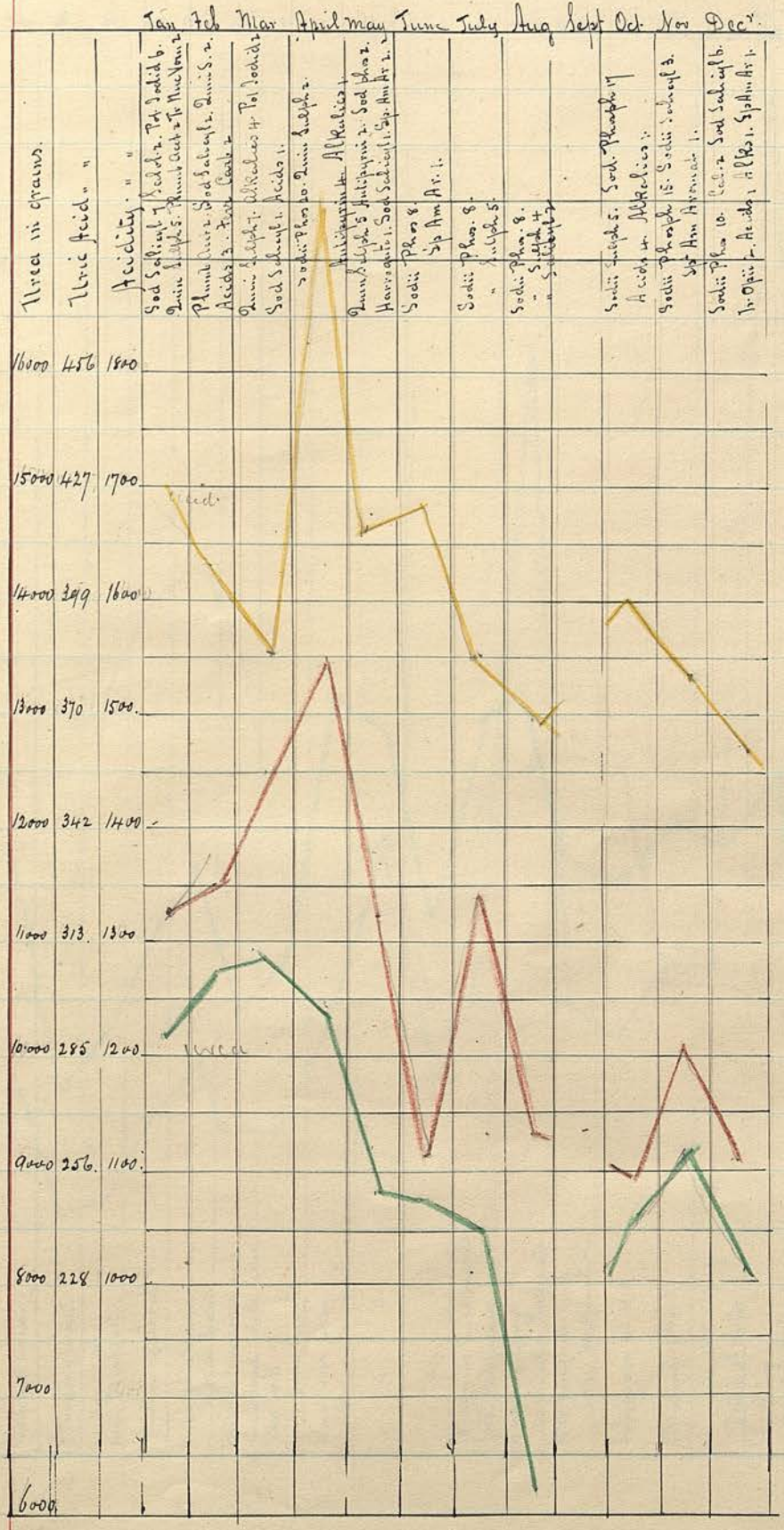


Fig 4. Showing Yearly excretion of Uric Acid from month to month natural fluctuations much clouded over by effects of drugs. Sept was a holiday

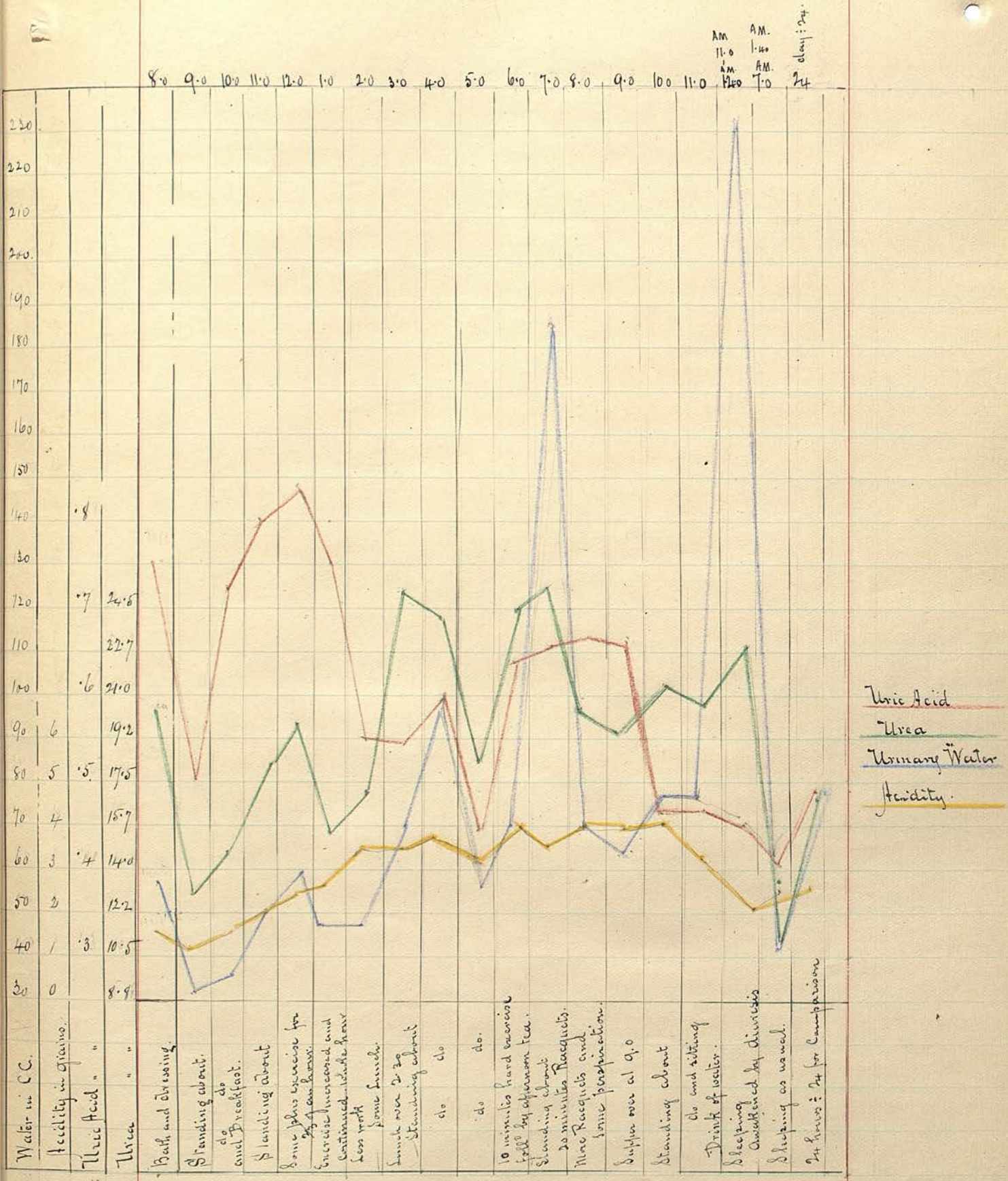


Figure 3. Daily excretion of Uric Acid from hour to hour.

Uric Acid can be Controlled by the administration of many substances which increase or diminish its solubility in the blood. It can be increased by direct administration of Uric Acid itself or of Xanthin or many of its Compounds which are practically equivalent to Uric Acid

Figure 3. shows much the same thing, only at greater length. It gives the actual hours to hours excretions of the hours of the working day. but it was obviously impossible to divide the night without interfering so much with physiological Conditions as to make the results of no value.

Figure 4. is an attempt to show the annual fluctuations in the excretion of Uric Acid.

What we see in this figure is that speaking generally. the warm months of the year Correspond to the morning hours of the day. and show a relatively large excretion of Uric Acid. and it follows from our first principles. that they should do this. for Acidity. is diminished in them all by an increased loss of acids from the skin. in perspiration. Conversely the cold months of the year. Correspond to the evening and night-hours. as in them the acidity is raised. by a diminished loss of acids. from the skin. and with this we see a diminished ~~loss of acids from the skin~~ excretion of Uric Acid."

Dr Haig found out that by influencing the solubility of Uric Acid. he could do almost anything he liked with its excretion. "That by Controlling

" the amount introduced. into the body. I could exercise still further. and still more decided control over the amount that could pass into and through the blood.

He divides drugs into 2 Classes in relation to Uric Acid. (1) those that increase (2) those that decrease

(1) the excretion of Uric Acid. (1) Those that increase excretion are. Alkalies. Salicylic Acid. and its Compounds. Salicin. Salol. Phosphate of Soda. Piperazine Quinine. Belladonna.

Speaking generally. and apart from the action of other solvents. it seems that excretion of Uric Acid from day to day. and hour to hour. is inversely as the acidity of the urine. Corresponding both in direction and extent with fluctuations in the alkalinity of the blood.

(2) The chief substances which decrease the excretion of Uric Acid. are Acids Iron. Lead. Mercury. Silver Copper Zinc. and other metals. Lithia Magnesia Calcium Chloride and other salts of Calcium. 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. the Iodides Antipyrin. Ammonium the nitrites. some hyposulphites. Strychnine &c

All these substances diminish 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. - also into the Liver Spleen and other organs.

He concludes (p105). the supposition that these substances act on the circulation by their effect on the Heart & Vessels. or both or by influencing Certain Nerve Centres. in the Brain or Cord.

He says with reference to Opium (105). "To say for instance - that small doses of Opium in producing mental stimulation and well-being. act direct on the vessels or Nerve tissue is Ithink to talk nonsense. and make two Causes for one effect. when one will suffice. Opium as I have shown clears the blood of Uric Acid. which permits relaxation of arterioles and Capillaries. all over the body. and alters the circulation from the Crown of the Head to the sole of the foot.

On pp. 109-114 he sums up his position in 9 propositions which are too lengthy to quote.

Uric Acid. and Metabolism p136.

Perhaps the most striking feature of originality is that metabolic changes. in which others have looked for the source and origin of Uric Acid are attributed by Haig to the action of Uric Acid itself. As an instance of the influence of Uric acid on the general metabolism he says. Uric acid is commonly in excess in the blood. because that fluid is more than usually alkaline. (i.e a more than usually good solvent of Uric Acid). but the effect of an excess of Uric Acid

on the blood. is a diminution of the capillary circulation. in all the organs and tissues of the body. and as results of this we get among other things diminished digestion and absorption of food. and a diminished interchange between the blood and the tissues. That is a general slackening of Metabolism and this in turn brings about a lessened formation. of ~~Uric Acid~~ Urea. and of acids and acid salts. which usually keep pace with Urea. But falling acidity means. increased alkalinity of the blood. and so long as plenty of urate is available. for solution. — more and more marked uricacidaemia. and thus depression of mind. body. and metabolism gets worse and worse. and there seems to be no end to it. —

But if a drug be given which clears the blood of Uric Acid. the process. may be quickly. and completely reversed. "up goes the formation of Urea and of acids a steady and progressive metabolism is started and the blood is kept clear of Uric Acid" That is the answer to the question. Why does a very minute dose of a nitrate. a few grains of a sulphate. or a small portion of a grain of Calomel. relax the arterioles all over the body. and cure Headache & Mental depression?

He sums up. the chapter on Metabolism as follows Uric Acid acts as a factor in the causation of disease.

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

(2) the contraction of arterioles and capillaries. affecting on the one hand the circulation, nutrition, function and temperature of all the organs and tissues of the body and on the other producing high blood pressure. which directly affects the Heart and vessel walls. and otherwise ~~affects~~. influences the intra-cranial. thoracic and chylopoietic circulations

We shall see that by this action on the circulation it controls the physiology of every-day life and determines the slow or quick combustion of the human body. just as shutting or opening the flues. determines that of the Kitchen fire

Pulse Tension.

He quotes Ewing's statement (Megrim p 329). that several observers have noted that the pulse during an attack of Megrim is slow and of high tension He had already determined that this Headache was due to Uric Acid. by influencing which he could remove the Headache. and when the amount of Uric Acid was altered, so also the rate and tension of the pulse was altered. He therefore formulated the conclusion that "Ceteris 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"

Uric Acid caused the Headache. the high tension pulse. and cold extremities. That the slow pulse was the result of the high tension was in accordance with

Marey's Law. that pulse rate varies inversely as arterial tension. Thus he says "(Le coeur bat d. autant plus frequemment qu'il éprouve moins de peine a se vider). The Heart as much more frequently as it experiences less difficulty. in emphying itself another he gives as to explain that the chief obstacle to the Heart's Systole is the resistance "(que le sang éprouve a s'ecouler des artères dans les veines à travers les petits vaisseaux). that the blood experiences in gliding (flowing). from the arteries into the veins. through the little arterioles vessels.. and again he says. "(La vitesse du sang augmente. si la force du coeur augmente ou si la resistance des petits vaisseaux diminue"). The speed of the blood increases if the force of the Heart increases. or if the resistance of the arterioles diminished). and then he expresses the effect of the arterial tension produced by the resistance in these little vessels on the rate of the Hearts action by saying "(le coeur précipite ses battements. à mésure que la tension arterielle leur fait moins d'obstacle") The Heart quickens its beating in proportion as the arterial tension. causes less obstacle (opposition) to the ~~heart~~ its). Then as to the signs of high arterial tension he mentions " pulsations rares. le coeur se vide difficilement, le punctation du sang dans les artères est lente. - le dicrotisme n'a que peu d. amplitude (and again) Le resserrement des petits vaisseaux. cause primitive de cette tension elevée des artères se traduit par la diminution du

volume. des extremités par la moindre coloration des tegumants. par l'abaissement de la temperature peripherique. (Circulation du Sang pp 315-356.)

(translation) infrequent pulsations, the heart empties itself with difficulty. the flow of the blood into the arteries is slow. dicrotism is only of small amplitude. The Contraction of the arterioles primitive original Cause of this raised tension of the arteries. is manifested by the lessened volume of the extremities by the lessened coloring of the tegumants and by the lowering of the peripheral temperature." in a word all the signs of the Uric Acid Headache. and the conditions to which it is related.

Hefinds Confirmation for his Theory. in what Sir W. Roberts (Urinary & Renal Diseases p71) calls the alkaline tide. 6 or 7 am to 2 or 3 pm. in which the quantity of Uric Acid secreted. is 3 times as large as at other periods of the day. and maintains that his Fig 3. illustrates this. - that Uric Acid is in excess in the blood daily from 4 or 5 am. to about 2 pm. and that it is more or less completely absent from it from 2 pm to midnight. Also that by altering the acidity of the urine. ie the alkalinity of the blood. - say by a few doses of an Acid. we can completely prevent there being any large excretion of Uric Acid in the morning hours. Similarly a few doses of Pot-Citrat will bring a great quantity of Uric Acid through the blood.

From the above Statement that arterial

Tension varies with the amount of Uric Acid that is circulating in the blood. and arterial tension Controls the rate of the Heart's action (Marey). Therefore the pulse ought to be of higher tension and therefore slower in the early Am hours. and up to about 2 pm. and of lower tension and therefore ~~slower~~ quicker in the pm hours and up to midnight.
the qualis (Marey in Confirmation "(Circulation du Sang p.350)
On observe le matin au reveil. un ralentissement du pouls. avec tous les caractères de la forte tension: le soir au Contraire. le pouls s'accelere et presente la caractère de la tension faible.) - the notice in the morning on waking. a slowing of the pulse with all the characteristics of high tension. in the evening on the Contrary. the pulse quickens. and presents the marks of low tension. therefore also. the arterioles and capillaries are most contracted in the above mentioned Am hours. and least so in the pm hours.

The above is confirmed by independent testimony from the Kidneys as is shown by Fig 3 and almost all the other Curves. he gives. which show that the urine is scanty in the Am hours. and up to 2 or 3 pm. and limits to the profuse in the pm hours which follow.

Since faradising the central end of the Vagus. Causes contraction of the Renal Vessels, and Consequent stoppage of the flow of urine. (Brit. Med. Jour. Epitome p 104 1895). therefore contraction of the renal-vessels. diminishes the flow of urine. and dilation increases it. Therefore physiological contraction. is greatest in the hours in

which Uric Acid most exceeds its normal relation to urea and Conversely. He shows (p 144)

That the arterioles and capillaries are Contracted by the Uric Acid in the blood. is Completely demonstrated Fig 3. . that urinary water varies from hour to hour. and day to day. throughout life. - alike in physiology - drug action - and pathology. inversely with the height of Uric Acid above its normal relation to Urea.

He illustrates his Contention by reference to Dr Lauder Bruntons experiments with the administration of Digitalis and Erythrophlaeum, showing that these drugs Cause Contraction of the Renal arterioles and a Consequent rise in blood pressure. and pulse tension and at the same time a diminution of urinary water. and that as the tension falls. a copious diuresis begins (Brunton. Pharmacology. 3rd Ed p 430). Dr Bruntons Figure (fig 32). is very instructive for it shows that in the case of Digitalis and drugs of similar action "the diuresis has been wrongly credited to rise of pressure which Dr Bruntons 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"

Dr Haig claims that the Course of events in the experiments. with Erythrophlaeum and Digitalis are exactly parallel with what occurs in the

Uric acid Headache. Epilepsy. Hysteria and other Conditions accompanied by high-tension pulse and contracted arterioles.

He maintains that what happens in the Kidneys during plus existence of Uric Acid in the blood might apply word for word to the excretion of water from the Lungs. where arterioles and capillaries "own to being contracted in exactly the same way. and in exactly the same relation to the excretion of Uric Acid" (p 145).

He next considers how excess of Uric Acid in the blood produces contraction of arterioles and capillaries throughout the body. and thinks there are 3 possibilities.

3 possibilities

(1) Uric acid may act as Erythrophlaeum and Digitalis do in the vessels of an artificial circulation, in the Case of Erythrophlaeum after division of the cord. so that all question of any action on the Vaso-motor centre is removed.

(2) It may act directly on and through the Vaso-Motor Centre

(3) It acts on suggestion (as he thinks but Roberts suggests it also). Uric acid in a colloid form may block arterioles and capillaries. It is just possible. this condition or something very like it "may occur just when there is a change of solubilities or a balance as it were between alkalies on the one hand and acids on the other (p 147). Roberts (Croonian Lect 1892 p 118) says of the possibility of gelatinous precipitation. "In Man and Mammals. the production of Uric

Acid is all too small to furnish, under any circumstances, a solution sufficiently concentrated to throw down the urate in the gelatinous form. In all my experiments on the behaviour of Uric Acid with blood serum and Lymph. I have never seen the least indication of precipitation except of the far less soluble crystalline Biurate."

Haig next proceeds to show how the various drugs which clear the blood of Uric Acid act beneficially by insisting that clearing the blood of Uric Acid means freeing the circulation and quickening Combustion and metabolism throughout the body, affecting alone and the same time, such different organs and tissues as the skin brain, lungs, stomach, Kidneys Uterus.

He considers the very essence of his argument to consist in the fact which he maintains he shows all through his work, that "physiological uricacidaemia can be diminished or controlled by altering the diet and that when this has been done, its pathological effects will be diminished and postponed, and chief among these is that gradual failure of Combustion, metabolism and nutrition which we call Chronic Bright's disease, as it is a mere prolongation or accentuation of the diminished Combustion which is the result of all "Uricacidaemia."

He considers that his proposition that Uric Acid acts on the arterioles as above stated by Constricting them and so raising blood pressure

and pulse tension. is irrefragably and absolutely proved. by the observed fact. that urinary water. Varies from hour to hour and day to day. both in physiology and pathology. inversely with the Uric Acid. excreted along with it.

Any one can convince himself of this fact- who will take the trouble to estimate excreta for a few days and Sir Henry explains the sequence of phenomena thus

An excess of Uric Acid over Urea in the urine. Comes from an excess of Uric Acid in the blood. and and excess of Uric Acid in the blood. Contracts the arterioles and diminishes the excretion of Water. just as we have seen that Digitalis and Erythrophlaeum do. therefore Contraction of arterioles or obstruction of Capillaries is directly as the Uric Acid in the blood., and Remembering Marey's law. pulse-rate is inversely as arterial tension therefore pulse-rate is inversely as the Uric Acid in the blood.

He maintains next. that the contraction of arterioles or blocking of Capillaries. a more mechanical action. — is a far better explanation of Migraine with high blood pressure. than any theories that invoke the action of nerve centres or the action of the abdominal sympathetic. and asks "in physiological conditions what possible source of Vaso- Motor irritation is there in the AM. and early PM hours. which is absent in the

later from hours. or why does a dose of Calomel affect the blood pressure at any time. ?
(a non purgative dose I suppose is meant).

He next considers the theory that high-blood-pressure (as held by the late Dr King Chambers). is due to waste products in the blood. - is not very far distant from his theory that it is due to Uric Acid

The evidences of high-blood pressure are-
(p176) "Where there is Bradycardia. that is where the Heart does not complete more than 60 cycles. in a minute. where the radial artery rolled under the points of 3 fingers feels full between the beats and the pulse gives a tracing as in fig 37. where the first sound of the Heart is long. and the 2nd sound. both at the apex and over the aortic area is loud. and where also the skin and extremities tend. to get easily cold. and the urine and other secretions tend to be scanty. where the temperature in the mouth and rectum tend to be far apart. and are perhaps. also both of them lower than in the corresponding hours of a normal day. - there can be very little doubt about the presence of high blood pressure. and where it is present. and there is reason to believe that it is doing harm the obvious indication is to reduce it

All the drugs previously mentioned as diminishing excretion of Uric Acid in the urine will when they do this - lower the blood pressure

quicken the pulse. and free the circulation throughout the body. Metals and their salts. which form insoluble Compounds. with Uric Acid will do this best. but these only clear the Uric Acid. out of the blood. into the tissues, and when they are left off. and the condition of the blood becomes suitable they get back into the blood again and the Patient is worse than ever.

He recommends a course of Salicylates for five or ten days. to Carry off the stores of Uric acid accumulated when the circulation is free or a course of Acids and salicylates given alternately.

Histogenous Theories.

Theories of a Primary. Dyscrasic tissue Change.

These deal with the link which must exist between the structural and chemical pathology of Uric Acid manifestation. No one has as yet fully succeeded in explaining this. Though those theories which attempt to define the Connexion between tissues and their juices. and their mutual behaviour. deserve greater attention especially valuable in this relation was the suggestion of Laycock. that "Gout was not of necessity always articular. or even always Combined with joint trouble and that a production of Uric Acid in the tissues rather than in the blood was characteristic of Gout."

Theory of Parkes and of Barclay.

A A Primary alteration in the metabolism of the Blood or of the Tissues

Parkes (On Urine 1860). While admitting that the Kidney was responsible for the retention of Uric Acid. he recognised a retarding influence in "important alterations in metamorphosis (metabolism?). in the blood. or in the tissues the abnormal products of which might be capable of holding back. Uric acid. and other substances such as phosphoric acid.

Barclay (On Gout and Rheumatism in relation to Diseases of the Heart 1866). attributed the failure of the Kidney. to excrete Uric Acid to "a primary change in the blood Corpuscles. directly due to a faulty diet till one after one became affected and the Gouty state induced. The retention of uric acid is to be regarded as a symptom. a Consequence of the attack of Gout and not as its Cause." This theory is interesting because the Red Blood Corpuscle is selected as the origin of the evil. just as its Companion the Leucocyte is regarded in later theories

The step forward here Consisted in regarding the tissues as taking an active part in the formation of Uric Acid.

B Theories of Ord. and Ebstein

Antecedent Structural Changes Connected with the Chemical Changes

Dr Ord. (St Thomas's Hospital Reports 1872). Considers the primary fault which leads to the deposit of Uric Acid to be some essential defect inherited or acquired in the fibroid tissues. He also admits that the nervous

System - plays an essential part in the bringing about the deposit, more especially in the propagation of the gouty inflammation from part to part. When the gouty diathesis exists, any sudden excitement of the Nervous System can produce gouty inflammation in a violent form and in several parts at one time. He considers Gout to be "a mode of decay of the whole system, that the deposit of urates is the result of local or general disintegration the local inflammation not necessarily depending upon such deposit, but often set up by local exciting causes, that the local inflammation and degeneration tend to infect the rest of the system through the blood, and to set up similar actions elsewhere through reflex nervous influence."

Ebstein's Theory.

Falls naturally also into this division. It has attracted a good deal of attention if we may judge by the number of times he is quoted throughout the literature of the subject, and his work. "Die Natur und Behandlung der Gicht" has been translated into French and mentioned with approbation by Charcot.

As we have mentioned already, he considers Uric Acid to be formed in those parts of the body, which normally take no part in its formation. (disproved by Horbaczewski's experiments). viz. muscle and bone marrow. When it accumulates to such an extent that it exists in a concentrated form in the blood, the tissues become infiltrated with it, in the form of a neutral urate. This acts as a

Chemical poison. on the tissues. setting up necro-biotic changes. Such necrotic areas. act as "foci of reactive irritation on the surrounding parts." and thus cause the phenomena of the inflammation of a Gouty attack. The Uric Acid is deposited in the tissues only. when the necrosis has advanced to a certain extent. If it has not advanced to this degree. all local symptoms can disappear again and the joint may become as healthy as before. The deposit of urates therefore according to this Theory. occurs. only in areas which have become completely necrosed. and is secondary to the previous Concentration. infiltration and necrosis., and is caused by the conversion of the neutral urate into. acid urate. by an acid supposed to be generated by the necrosed tissues. after their reaction has been changed from. alkaline to acid. by the necrosis. We have already mentioned. the fallacy. underlying his experiments. and would note further here. that as shown by the experiments of Horbaczewski Uric Acid is formed in all tissues. especially in those abounding in cellular elements. and further that neutral urates cannot exist. as shown by Roberts. because they can. only be produced in the presence of Caustic alkalis. and in the absence of Carbonic Acid and the Carbonates. We note too that Uric acid is formed in abnormal localities is an assumption no matter what experiments are made. if the basis of the theory is assumed not proved.

The Theory of the direct Histogenous

derivation of Uric Acid formerly hinted at by Laycock and by Parkes and taught more definitely by Ord did not reach maturity until Profr Latham worked out a chemical explanation of the process. and Horbaczewski demonstrated the steps in the transformation of Nuclein into Uric Acid.

Nervous Theories of Gout.

Stahl (1737) was the first to advocate a Nervous Theory of Gout. Dan Cullen (1784) considered Gout as "manifestly an affection of the Nervous system" and asserted that "Gout was more indicative of Nervous disorder than any other pyrexia". Sherlé in (1847) thought the origin of the condition would probably be found in the Central nervous system. Profr Gardiner (1849) favoured a Neuro-humoral theory teaching that the defective elimination of Uric Acid was due to some more distant Cause and found suggestive analogies in the check to the renal function induced by shock emotion hysteria. Dr Ewing (1873) suspected a nervous origin in Gout from the paroxysmal and periodic features of the attacks. But the most doughty champion of the Theory that Gouty manifestations are a Tropho-Neurosis is

Sir Dyce Duckworth (A Treatise on Gout 1889).

He boldly affirms at the outset in his book "No Uric Acid No Gout" and that whatever be the views entertained as to the whole pathogeny of Gout the facts discovered by Sir A Garrod cannot be

set aside. He questions whether the the theory of excess of Uric Acid. is sufficient to account for all the phenomena of Gout. He quotes with approval Guirdner's (a supporter of the Nervous theory). dictum. "The gouty diathesis is often very well developed in individuals who never see its local manifestations" — He stands firmly by the position that gout owns a nervous as well as humoral pathogeny. (op cit p 20). It is something beyond the resultant effects of the abnormal retention of Uric Acid (p 21).

He regards Gout as a hereditary Neurosis.

Habitual or prolonged excess develops hereditary tendency. He defines a Neurosis as a "peculiar disposition or tendency on the part of the nervous system or some definite tract of it toward morbid evolution or manifestation of Nerve function". and sees nothing more absurd in a man inheriting a certain nervous physiognomy than in inheriting a Roman Nose. (p 25).

In upholding the neural factor in gout he points to various features which are characteristic of Neural affections or Neuroses. (Epilepsy. Angina pectoris Asthma Neuralgia) such as periodical tendency. onset in the early morning hours. alternation manifestation and liability to be induced by Nerve excitation or depression

He is not prepared to accept wholly physical view. nor is wholly chemical theory adequate. for a really comprehensive view the marked determining influence of the Nervous factor is necessary (op cit p 49)

Diseases belonging to the Neurotic type may be either primary or central or may be secondary or induced and he alleges. Gout. presents many of the characteristics peculiar to the Neuroses. eg. hereditty periodicity. instability and alternations in its manifestations eg. Gout and Epilepsy. Gout and Diabetes and a liability to be induced by. nervous changes. & Conditions Primary Gout he regards as a diathetic Neurosis. but he finds it not so easy to account for Gout occurring where there is no Neurotic element.

He assumes that at least in some of these a Condition of lithaemia and hyperinosis is set up. as a result of high living and that the consequent dyscrasia of the blood. reacts upon the Nerve Centres ie. a secondary affection of some Nerve Centre occurs in consequence of the altered state of the blood. and thus the order and special phenomena. of the Gouty attack become developed. He thinks that one-sided manifestations of arthritism. which have been well established in certain cases as joint affections Rheumatism. neuralgia. indicate still further a dominating Nervous influence. (p49).

"Gout is a hereditary Neurosis. Habitual or prolonged excess. develops hereditary tendency, Undue mental labour. alcoholic intemperance, debauchery. and other indulged. evil propensities in the parent. come to be developed into a definite neurotic taint. and tendency in the offspring. therefore Gout appears as a Diathetic Neurosis" (p 24) The Parkes have eaten sour grapes. &c.

But there are other indications besides heredity and periodicity which seem to indicate a Neural factor in Gout and ally it with the neuroses. such as. the sudden supervention of the attacks. the preceding sensation of vien-être. the time of attack... and paroxysmal character. the connection of the disease with other well recognised neuroses.. and the fact that the same causes are liable to excite attacks. all these indicate the close relation which subsists between Gout and the Nervous system.

Sir D Duckworth then combines the humoral and Neurotic elements in his theory. He says. "I cannot dissever the two ideas. and hence I affirm that Gout is a Neuro-humoral disease. No where in health is Uric acid met with as such... Its presence in tissue or secretion is a sign of disease"

Still he looks beyond the Chemical pathogeny of Gout for a "presiding nervous element". and he finds it in the neurosis which may be either implanted that is primarily impressed as an individual heritable feature or secondarily induced owing to some toxaemic condition.

Sir Wollaughby Wades Neural Theory.

According to this theory Gout is rather a neuritis than a Neurosis. He finds patchy areas of acute tenderness over an inflamed joint which resolve themselves into narrow lines of acute tenderness in some cases extending beyond the zone of swelling and inflammation and which

Can frequently be recognised as following the lines of distribution of Cutaneous Nerves. He maintains that the aching and tenderness over an inflamed joint can be shown to be independent of the movement of the joint. He inclines to regard the condition he has described as essentially Neuritic of which there are two kinds. implicating respectively the Conducting grey matter and the protective Coverings along two lines of extension. more commonly the upward extension as in Neuritis ascendens. the influence sometimes travelling up as far as the Cord itself. and sometimes a downward extension as in Neuritis descendens.

The etiological factor is an (assumed) alteration of the metabolism of proteids resulting in the formation of Quadriurate of Soda. which lowers the alkalinity of the blood. The disturbance of Metabolism is brought about by excessive mental strain. use of certain foods. especially alcohol in the form of fermented Malt liquours. By this faulty blood state the stability of the Nerve trunks is impaired and they are laid open to influences which would be inoperative on healthy Nerves.

From a consideration of the foregoing theories. we may safely say. that practically Dr D Duckworths. aphorism "No Uric Acid No Gout" has been accepted by the profession. as expressing its views. of the cause of Gout. though many differing

-views are held. as to its origin. physiology and pathology.
We now proceed to enquire. How Uric Acid
arises in the body. and what are the conditions
under which it remains physiological and what
are the factors which conduce to render it pathological.

Etiology. of Uric Acid.

Mach. (Archiv für exper Pathol. und Pharm 1887 p 148).

By feeding birds on Hypoxanthin. Mach found
that they excreted larger quantities of Uric Acid
and concluded. that Hypoxanthin must be an
intermediate stage. in the disintegration of Albumen
into Uric Acid. This may be so in birds. where the
final stage of nitrogenous metabolism as found in
the urine is almost entirely Uric Acid. but in
Mammals the final stage. of the Metabolism of
Albumen. is normally Urea.

By ligaturing the vessels of the Liver. and finding
no change in the production and formation of Uric Acid
he showed. Uric Acid was not formed in the Liver.

Maccss. (Quoted by Husch - Virchows. Jahresbericht (1889) p 145)

Showed that in every individual. after the
13th hour of fasting. the excretion of Uric Acid remains
almost Constant but that after a meal. the
excretion of Uric acid rises rapidly and sinks
again after several hours. The amount of Urea
excreted. does not begin to rise. till later. and
attains its maximum nine hours after the meal,

And then falls again: Therefore he concludes that Urea is formed from the albumens introduced in the form of food, but that Uric Acid is formed from the tissues of the body and that the increased Uric Acid produced after a meal does not arise from the albumens of the food - the digestion of which has hardly commenced - but from the increased cellular activity.

Horbaczewski proves Uric Acid is formed in nucleins

Horbaczewski. (Beiträge zur Kentnisse der Harnsäure und der Xanthin Basen., Sitzungsbericht d. K. Acad. d Wissen. in Wien. Abth III April 1891).

and his pupils show that Uric Acid as well as Xanthin and Hypoxanthin can be prepared from the tissues, and with especial facility from the Spleen. This had been stated long before by Parkes. (Lancet. 1871 I. 467). who suggested that Uric Acid and Urea were formed by separate processes, and that the spleen was the seat of origin. He was led to adopt that theory by the study of several cases of enlarged Spleen which were attended by a nearly four-fold excretion of Uric Acid. This seems to be confirmed by the fact that the Spleen acts as a diverticulum for the accommodation of a relatively large quantity of the blood, upon which those active metabolic processes take place, which constitute a special function of the spleen. After every meal it is in a state of more or less congestion, or hyperaemia.

which reaches its maximum about 5 hours after taking food. after which it returns to its normal bulk. It should be remembered that this enlargement corresponds in time to the increased Leucocytosis and increased Uric Acid excretion about to be mentioned.

"When fresh spleen-pulp is rubbed down (Levison The Uric acid with 8 to 10 times the amount of distilled water. and the Diathesis p 20) mixture left standing at a temperature of 50°C. for 8 hours. Bacteria gradually develop. numerous gases are produced. and towards the end of the experiment. a slightly foul odour becomes apparent. The experiment must then be interrupted otherwise. further products of decomposition occur.

By digesting in this way, the greater portion of the spleen tissue is dissolved, and on separating the undissolved portion. and precipitating with Lead Acetate the albuminous bodies are removed. and the fluid sterilized. Nitrogenous substances. are now found in the Solution and appear to be forerunners. of Uric Acid as well as of Xanthin and Hypoxanthin, but their chemical Composition has not yet been accurately ascertained. and they have not so far been isolated When the fluid is heated and again filtered, and the filtrate Condensed. by evaporation to a small volume. Xanthin and Hypoxanthin but no Uric Acid are found in it. Guanin and Adenin, which former investigators have prepared from spleen pulp.

were not found in the solution. because by the decomposition Adenin is transformed into Hypoxanthin and Guanin into Xanthin.

If the fluid obtained by precipitating with Lead Acetate is heated at 40° - 50° C. with an equal volume of arterial blood or a dilute solution of Peroxide of Hydrogen. Uric Acid forms in it. after several hours. The same result can be obtained with an abundant supply of atmospheric air. About 2.5 mgrms. of Uric Acid can be formed from 1 grm of spleen-pulp.

Xanthin bases. Cannot be oxidised into Uric Acid

"It follows from these experiments that substances exist in the spleen. which are easily decomposed. and that by this decomposition. nitrogenous compounds are formed. which can further be transformed. into either Xanthin and Hypoxanthin or into Uric acid. When however Xanthin bases are formed. no further oxidation into Uric Acid is possible.

The question next arises. What Constituents of the Spleen Can become decomposed. into Xanthin bases or Uric Acid?

It had formerly been supposed that this mother substance was the nuclein of the lymphatic Constituents of the spleen and Horbaczewski has now brought forward. proof of this.

"Fresh Spleen pulp was digested. with a strong acid solution of pepsin for about 24 hours. at 37 - 40° C. The fluid in which most of the nuclein. was suspended was shaken up with Ether The nuclein settled on the top of the watery fluid. below the Ether as a dense grey layer. It was then removed from the fluid again shaken up with water. and Ether and with alcohol. as long as it coloured it, digested at 40° C. and extracted with Ether.

It then appeared as a grey powder which on microscopic examination was found to consist of pure nuclein. - Horbaczewski was able to prepare Uric Acid by dissolving this nuclein in a very weak lye and treating it with blood at 40° C.

nuclein oxidised into Uric Acid.

As the nuclein when treated in this way decomposes very slowly the task is more readily accomplished when the solution is heated with water and a weighed quantity of spleen pulp. It is then easy to calculate the amount of Uric Acid arising from the nuclein by comparing it with the quantity of Uric Acid obtained from the same quantity of spleen pulp alone -

Uric Acid from other organs besides the spleen

Further experiments showed how far Uric Acid could be obtained from other organs and tissues. Sadowenji and Formanek. Horbaczewski's assistants treated a large number of organs of men and calves in the same way as described in the case of the spleen and found that Uric Acid was present in almost all the tissues of the body in Mucous Membrane of the bowels - bone-marrow - thymus - liver muscle - lung brain Kidney skin It was shown at the same time that these tissues, and the blood used in the experiments did not normally contain Uric Acid, and if so only in traces. As all the tissues corresponded to the spleen in the preparation of Uric Acid - and as either the xanthin bases or Uric Acid could at will be prepared from them it can no longer be doubted that in the case of these organs also the nuclein contained in the cells is the mother substance

nuclein with food injected subcutaneously excreted as Uric Acid.

Accordingly Horbaczewski and his pupils having shown that outside the system Uric Acid

Can be prepared from the Nuclein present in all the tissues of the body. the only question now was whether a similar decomposition also took place in living human beings. In order to settle this. Horbaczewski first investigated how nuclein acted when it was introduced into the body. The investigation showed that the excretion of Uric Acid can be increased both when the nuclein is taken with the food and when a solution of it is injected subcutaneously. A weak alkaline solution of .75 grm. was injected subcutaneously into a rabbit and in the place of the normal 7-8 milligrm. it excreted 25.8 milligrm of Uric Acid in 24 hrs

A man ~~who~~ was fed during the experiment for 5 days on a regulated diet. Consisting of flesh bread. butter. &c. and the production of Uric Acid reached. .689 to .861. grms per day. Ten grms of Nuclein were then given to him daily in addition to his food. and the Uric Acid rose to 1 grm..

The day after taking the Nuclein it was .957 grm and again gradually diminished. In this case there was not a very considerable increase. It is more striking when the Nuclein is administered during fasting. As Maress. has shown. during fasting the excretion of Uric Acid falls. during the first twelve hours. and the minimum so reached. remains unchanged. from about the 14th hour.: if during this period of equal production Nuclein is administered and the fasting continued. the excretion

of Uric Acid is thereby considerably affected

A man fasted 18 hours. and then took 5.5 grms of Nuclein suspended in water. The amount of Uric Acid and the total amount of nitrogen were estimated every 2 hours. and the result will be seen from the following Table.

Hours.	Amount of Urine	Nitrogen	Uric Acid
9-11	81 cc	1·065 grm	46·8
11-1	670 "	1·040 "	46·9
1-3	335 "	1·013 "	64·7
3-5.	148 "	1·096 "	93·6.

Nuclein was given at 11.

A second experiment gave similar results. therefore on administration of nuclein by the mouth the uric acid excretion is increased. ~~Nuclein~~ The delay is explained by the slowly digesting nature of Nuclein

It is most probable. from these experiments that Uric Acid is formed in health by the disintegration of Nuclein which exists in different quantities in all tissues of the body. All the constituents of the tissues cannot be so rapidly disintegrated that a sudden variation in the Uric Acid production can be explained in this way. This can be true only of the Leucocytes which are present in the blood, lymph, Connective tissue, glands. in short everywhere in the body. If a large meal (corresponding to the alkaline side of Roberts). is able to cause a considerable increase in the number of Leucocytes in the blood and this increase after a few hours disappears it is reasonable to suppose that the cells have become broken up. and the nuclein contained in

there converted into Xanthin bases. or Uric Acid within the system. This hypothesis is also supported by the fact demonstrated by many observers. that a temporary or permanent leucocytosis is always accompanied by a corresponding increase in the amount of Uric Acid (or Xanthin bases) formed in the body.

In childhood the blood is richer in Leucocytes owing to the more active metabolism, and the production of Uric Acid is also greater than later in life. The Nitrogen of the Uric Acid reaches in the first day of life 7-8 per cent of the total Nitrogen eliminated. while in adults it is only 1-2 per cent.

As already stated the excretion of Uric Acid in adults is diminished during fasting and rises after taking food especially flesh food. The behaviour of the White Corpuscle corresponds to this. their number sinking to a minimum after 18 hours fasting. where they remain if fasting is continued. and then again rising considerably 2½ hours after a meal

According to Mares. (Hirsch-Virchow's Jahresb. 1887. p 145). The excretion of Uric Acid remains unchanged from the 15th to the 27th hour of fasting. while the absolute amount varies according to the individual After a meal abounding largely in Flesh food. the amount of Uric Acid excreted immediately rises and reaches its maximum in 5 hours. after this it sinks and 12 hours later is again at the level from which it started. The production of Urea rises more slowly reaches its maximum 9 hours after food and sinks again more slowly

Roberts experiment

Roberts (Edin Med Jour. 1860 p. 817 and 900) determined by experiment, that after 6 hours sleep and 16 hours fasting the urine of a healthy man who had eaten two good meals was strongly acid. yet did not contain much Uric Acid From 3-4 hours after food urine was less acid - sometimes alkaline but contained much more Uric Acid

Krabaczewski's experiment on 5 healthy men showed. (after fasting and then a good meal). a very great increase in the number of White blood Corpuscles and Uric Acid. This increase in the number of White blood Corpuscles in the blood after a meal is to be explained only by leucocytes being formed in large numbers in other parts of the body and passing into the lymph stream into the blood.

Individual examined	No of Leucocytes after 18 hrs fasting	Urine passed between 6 & 18 hrs fasting in cc.	Amount of Uric Acid in milligrams	Total nitrogen in milligrams.	During Fasting
1	4500	140	39.9	1034	
2	4750	50	42.5	642	
3	5002	120	49.6	1056	
4	9950	50	57.2	756	
5	5700	160	33.3	463.	

	No of Leucocytes 5 hours after taking food	Urine after 4 and 5 hours after taking food in cc.	Amount of Uric Acid in milligrams	Total nitrogen in milligrams	After taking flesh food.
1	7250 = + 61.1%	340	148.1 = + 271%	1445	
2	7500 = + 57.9%	85	117.3 = + 176%	1014	
3	7744 = + 54.8%	330	143.2 = + 188%	1838	
4	14900 = + 49.5%	260	106.0 = + 86%	1445	
5	7700 = + 35.1%	85	102.0 = + 206%	925.	

					During Fasting
1	4500	140	39.9	1034	
2	4750	50	42.5	642	
3	5002	120	49.6	1056	
5	5700	160	33.3	463	

				After taking vegetable food
1	5900 = + 23.1%	95	44.4 = + 94%	869
2	4900 = + 3.1%	55	52.9 = + 24.5%	793.
3	5050 = + .95%	280	59.3 = + 19.5%	1159
5	5850 = + 2.5%	290	42.3 = + 27%	1086.

I have placed these two tables one under the other to facilitate comparison of the amount of Uric Acid and number of Leucocytes after a mixed (mainly flesh) meal and a meal entirely vegetable; as some assert that the increase in Uric Acid takes place after a flesh meal only. These tables show that Leucocytes and Uric acid both increase as well after meals of vegetable food as after animal food.

Note that only in one of the individuals was there Considerable increase in the excretion of Uric Acid after a meal of vegetables and this increase was accompanied by an increase in the number of Leucocytes. On the other hand the difference in the total amount of Nitrogen eliminated after both meals was much more limited which strongly points to the probability that the increased excretion of Uric Acid is due to Leucocytosis and not to the disintegration of albumen introduced as food

In individuals in whom no digestive Leucocytosis takes place or does not make its appearance till very late there is no increased excretion of Uric Acid, or it only appears much later after the meal than usual. as Stolnikow showed by repeating the above experiment on 2 patients suffering from Carcinoma Ventriculi.

These experiments show that the excretion of Uric Acid is of unequal amount in different individuals and in them is affected by influences which diminish it as fasting or increase it as flesh food.

The fault with Stolnikow's experiments is that one does not learn from them how the urine

passed during the whole 24 hours was influenced by the different foods. The experiments of Bleibtreu and Schultze. (Pflugers Archiv. Bd 45 p 401). supply this deficiency. They determined their own total excretion of Uric Acid for 24 hours under vegetable and under animal diet. Bleibtreus results were

	After 3 days animal diet grms.	After 3 days vegetable diet grms
Total nitrogen excreted	24.4465	10.9217.
Urea.	47.3882	19.8082
Nitrogen in Urea	22.113.	9.2432
Uric Acid	0.859.	0.791.
Nitrogen in Uric Acid	0.2863.	0.2637.
Proportion of Urea to Uric Acid	1: 55.16.	1: 25.04
Prop^{n} of nitrogen of Urea to nitrog of Uric Acid	1:73.6	1: 35.05.

Schultze. whose habitual excretion of Urea per diem was carefully estimated. at 31.647 to 33.8549 grms. and of Uric Acid. at 0.836 to 0.844 grms. reached on successive days on

animal diet	Grms	Grms	Grms
Urea.	58.89	67.23.	73.65
Uric Acid	1.3886.	1.270.	1.473.

It is abundantly proved by these and other investigations. by. Unruhfeld (Virchows. Archiv Bd. 117. p 301). and Hardhagen that Uric Acid is formed by the destruction and disintegration of the Constituents of the body: processes which are decidedly influenced by the food. but not in proportion to the amount of albuminous substances Consumed. On the other hand the Urea excreted. can be doubled or increased even in a higher degree. If a large quantity of easily digestible albuminous food is taken,

In other words we see from the above tables that whereas the Urea excretion rises with almost mathematical accuracy with the amount of Proteids taken, the oscillations in the Uric acid excreted are much more limited and are not regulated by the diet.

So long as the generally accepted opinion was that the Uric Acid arose from oxidation of albuminous substances and could be changed by further oxidation within the body into Urea, it followed that of the total amount of nitrogen excreted within the urine, a certain portion was thrown out as Uric Acid and the rest as Urea. Many writers accepted the existence of such a constant proportion, and endeavoured to estimate the normal relation. Haig is one of the last that has arrived at such an estimate. (See article Haig's Theory) Vol 9. According to him the normal relation is Uric Acid : Urea :: 1 : 33 or 40.

The experiments of Stadthagenwski, Bleibtreu Schultze with how this theory. We feel compelled to draw the conclusion from them that the excretion of Uric Acid in each individual is a fairly constant quantity, changes in which indicate variations in the metabolism of the body.

Stadthagenwski's proposition that there exists a constant proportion between the excretion of Uric Acid and the number of White Blood Corpuscles in the blood gains additional support from the fact that the production of Uric Acid is increased by a whole series of diseases characterised by the formation and destruction of a large number of Leucocytes.

The influence of various disease processes and poisons on the production of Uric Acid

Leucocythaemia.

Laache. (Klinische Uranalyse p31) affirms that in this disease the amount of Uric Acid excreted can rise to 4 grms in 24 hours. and that he himself observed an excretion of 3·7 grms. in a case.

Bantels. (Deutsch. Archi f Klin Med. 1870 7 p13 Lenssen p33). notes a case with daily excretion of 4 grms of Uric Acid and another case with enormous enlargement of the spleen from which concretions from the size of a hemp-seed to a pea. were passed.

Bahland and Delsy. (Pflüger Archiv 47 p13) : found 1·22 grms. per day and 1·42 grms. on a later examination.

Stadthagen (Virchow Archiv. 109 p390) . compared the excretion in a healthy person ~~and~~ a Leucocythaemic and a pseudo-leucocythaemic and found the proportion of Uric Acid to Urea. to be 1:59 . 1:66 and 1:15·33). Food was nearly constant for the 3 individuals. He brought down the excretion of Urea. to 22·72 grms by vegetarian diet. while the Uric Acid remained unchanged. 1·91 grms. On a purely albuminous diet the Urea rose. considerably. but the Uric acid was not appreciably increased.

Febrile diseases especially Pneumonia are cited by Stokvis as being accompanied by Leucocytosis. and increased Secretion of Uric Acid. Similar conditions prevail in the early stage of Carcinoma. especially Carcinoma of the Liver. In one case Uric Acid varied between ·9 and 1·5 grms. per diem. and a like quantity is said to

be found in Commencing cirrhosis of the Liver. This however does not seem to agree with the lessened production in cases of Liver Abscess.

Burns In severe Burns an abundant secretion of Uric Acid takes place A boy of 15 (Lewisin p 35) who had more than ⅓ of his body Covered by burns gave off on the 3rd day .97 grms of Uric Acid on the 5th 1.22 grms. on the 7th 1.87 grms. Mason. while the total amount of Nitrogen was not unusually large.

Just as those morbid states which are accompanied by an abundant formation and disintegration of Leucocytes are also accompanied by an excessive excretion of Uric Acid so Horbaczewski has found that those drugs and poisons which increase the number of Leucocytes in the blood also increase the excretion of Uric Acid. and that various drugs of an opposite Class which prove of service in Leucocythaemia also diminish the Uric Acid excretion

Poisons. Certain poisons appear to increase the prodn of Uric Acid Bentels (Deut Archiv f. Klin Med 7 p13 Lewisin) noticed this in a case of CO. poisoning.

Phosphorus given to dogs (Frankel & Rohman) increased the amount of Uric Acid excreted. tho the same is not proved for the mammalia.

Pilocarpine quickly brings about a considerable leucocytosis Experiments on 4 healthy people (Lewisin 36). were made with the result that one hour after swallowing 10 milligrms of Uric Acid. the Leucocytes were increased 25 to 34.5%. In some cases after a few hours they were increased as much as 48% Shortly after this marked

rise in the number of Leucocytes. There was a corresponding decided rise in the excretion of Uric Acid - in one case from 33 milligrms. to 56 milligrms per two hours.

Alcohol. increases the formation of Uric Acid. Dr Chittenden professor of physiological Chemistry in Yale University published the result of his experiments on alcohol in "the" Dietetic and Hygienic Gazette. (quoted by the Medical Pioneer Nov 1896) These experiments show that the excretion of Uric Acid is always increased in a very marked degree by the consumption of alcohol. He calls attention to the fact that Uric Acid is always increased ~~in the urine~~ whether the total amount of nitrogen in the urine is increased a diminished Quantity. (Deutsch Med Woch No 10. 11). found by experimenting on himself. That the excretion of Uric Acid was always increased after partaking freely of alcohol. A similar testimony is given by Levison who also experimented on himself.

Exercise. -always. increases. the excretion of Uric Acid and. proof to that. effect. is brought forward by Levison p. 37. Hertig. (op cit. 256. 269). Bicycle exercise for. two hours always. Causes after excretion of Uric Acid in myself. experience.

Nuclein. always. Causes. increased excretion in a healthy person. proof of which has already been given ante.
Also. after a plentiful meal. consisting largely of flesh both the number of Leucocytes in the blood. and the excretion of Uric Acid quickly rises.
Horbaczewski showed that decided Leucocytosis was brought about by administrating Nuclein (vide ante p 8).

Grms. 5. suspended in water. increased the number of Leucocytes. in 3 sets of experiments almost 50%.
The patients experimented on had fasted for 18 hours before the nuclein was administered and took their first meal 2½ to 3 hours. later - the blood cells. having previously been counted. (the figures being 1st. 6800 - 12450. 2nd 4080 - 7350. 3rd 4800 - 7400.

Conclusions. (Luison p 38).

" From the foregoing history of experimental work we may draw the following Conclusions

(1) Uric acid is formed in the body. by the disintegration of the albuminous substances of its tissues. especially of the nuclein or Nucleins.

(2) The excretion of Uric Acid becomes increased or diminished by all factors. (diseases medicines. poisons). which give rise to a more rapid. or slower disintegration of the cellular elements of the body. and especially of the Leucocytes.

(3) The taking of food especially flesh food. Causes a temporary Leucocytosis. (digestive). this Leucocytosis probably arising from the nuclein of the food.

(4) The amount of Uric Acid excreted. in 24 hours is not influenced to a great extent by food. There is however this distinction noticeable. the easily digestible animal Albumens. set up digestive Leucocytosis. and formation of Uric Acid. much quicker than the vegetable albumens. which are difficult to digest.

Uric Acid in the blood. and the form in which it exists physiologically

Since Uric acid takes such a large part in the physiological and pathological processes of the Human body: it seems natural to enquire "what proof is there that it exists in the blood at all and in what form does it exist?

The answer to this was supplied by Garrod in 1848. who demonstrated the presence of Uric Acid in small quantity in the blood of healthy persons. and that it existed in much larger quantity in the blood of patients who were suffering from gouty inflammation. This as has been already mentioned is demonstrated to every student of medicine at the present day.

In cases of chronic gout Uric Acid can always be demonstrated in the serum. In acute gout it may be absent between the attacks. but can always be discovered shortly before they take place. One must not be so incautious as to diagnose gout invariably by such an experiment but should remember that there is great excess also of Uric acid in cases of chronic Lead poisoning and of certain diseases of the Kidney.

Uric Acid may. in addition to the blood be demonstrated in various secretions and fluids of the body. in the Gouty state. It has been demonstrated in the cerebro-spinal fluid. in the intestinal secretions in the effusion of Pleurisy and Pericarditis in the discharges from cutaneous eruptions. and in the form of dust. (Sodium Urate) in the skin.

Roberts (Bronchial Lect 1892. 83-4) has demonstrated

that Serum can take up Uric Acid in the proportion of 1 in 500. and that the greater the concentration of the Solution in the blood experiment the more marked the deposit of Crystals. Lewin obtained similar results in experimenting with Ascitic fluid. His results are quite in accordance with Garrods statement (Nature & Treat^t of Gout p 56.) that Serum containing '2 or more per thousand parts of Uric Acid shows abundant deposition of Uric Acid crystals.

Estimations of the quantity of Uric Acid in the blood

Salomon. (Chemie annalen 1878/218). found Uric Acid in the blood of 14 patients suffering from Pneumonia and Gouty Arthritis.

Von Jaksch. (Ueber die Klin Bestimmung der vorhandenen von Harnsäure u Xanthin Basen im Blute 1891). undertook the investigation of this question. with abundant material at his Command. Conducting his experiments with a solution of Uric acid which he injected into the blood vessels. He demonstrated that almost the entire amount of Uric Acid dissolved in the blood could be estimated. Haig's testimony is the same (Uric Acid as a factor in disease p). He says. he could recover in the urine almost every grain of Uric Acid administered to patients. (already quoted). op cit p 8) He (Vaut.) was unable however to find Uric Acid in the blood of healthy persons. He gives the results of the examination of the blood of 94 ~~healthy persons~~ patients. He found Uric Acid only in certain types of disease viz in Cases of Fever diseases connected with the Alimentary system

in Pneumonia. Kidney disease. the proportion of Uric Acid being particularly large. in cases of Granular Kidney and Uraemia. In cases of Anemia especially where the decrease of the Red cells. was accompanied by an increase in the White cells. there was great increase of Uric Acid. He explained this by the fact. that according to his Conception. most of the Uric Acid formed in the body. becomes further oxidised in the blood. by the activity of the Red Cells. If the number of these is diminished the Uric Acid remains unchanged. and is stored up in the blood as such"

From an examination of Van Jakschs table it is evident. that there is an excessive production. and active disintegration of the cells of the body. in almost all the Cases. in which he was able to find distinctly the presence of Uric Acid. in the blood. The increase of Uric Acid in the cases of Kidney disease was due probably. to decreased excretion. Though Von Jaksch explains his results differently from Horbaczewski. It is indeed from an analysis of his experiments that they are in favour of Uric Acid being a product of the tissue metabolism of the body. and derived from the disintegration of Nuclein.

The Chemistry of Uric Acid and its Compounds

Having that Uric Acid is formed in all blood. in proportions varying in Amount and demonstrably more abundant. in the blood of those persons. who either are the subjects of very active tissue changes. or whose excretory apparatus is defective. we now

proceed to enquire what chemical compounds it forms in the blood with the bases it there meets and unites with.

It is most commonly met with in the human economy as Bi Urate of Soda in gouty tophi: and it was formerly supposed that the lateritious deposit formed under certain circumstances in the urine was also this acid urate or Bi Urate.

Sir William Roberts denied the accuracy of this supposition and began to study this deposit. Most of our knowledge of the chemistry of Uric Acid and its compounds is derived from his researches. Our knowledge also of the behaviour of Uric Acid and its combinations both in the fluids of the body and after its excretion is due to his careful work.

We feel compelled to study somewhat extensively an account of his experimental work as correct treatment can only be based on correct chemistry.

He begins (Croonian Lectures 1892) by studying the amorphous urates of Human Urine frequently deposited in the urine of perfectly healthy people especially in the colder seasons of the year and at all seasons after sharp exercise, and after severe perspiration. It is also habitually seen in the urine of patients suffering from catarrhal conditions or trifling dyspepsia and is a common accompaniment of Pyrexia and of grave wasting organic diseases of all kinds It is found only in acid urine and is never thrown down in neutral or alkaline urine. It is recognised clinically by disappearing from the urine on heating.

Examined by the Microscope it appears granular and has no crystalline structure. It is a representative body. typifying the exclusive mode in which nitrogen is eliminated in vast tribes of the animal series.

It represents the Chemical Combination. and the sole combination in which Uric acid exists normally. in the healthy organism: and the pathological troubles connected with Uric Acid are due to deviations in one direction or other from this normal combination.

Uric acid is a dibasic Acid. $H_2(C_3H_2N_4O_3)$. and forms neutral and acid salts. Its Chemistry was worked out in Liebigs laboratory by Bensch and Allen (an English student). and has been unquestioned since that time.

Neutral Urates. Can only be produced in the presence of caustic alkalies. and in the absence of Carbonic Acid. and the Carbonates. Conditions impossible in the living organism We may therefore dismiss these from further Consideration.

Acid Urates. or Bi Urates. are the best known and most stable salts of Uric Acid. They are sparingly soluble in water. and are not decomposed thereby They are found pathologically as gouty Concretions chiefly as Sodium Bi Urate. It is never seen in health or disease as a deposit in unchanged urine. Only when urine undergoes Ammoniacal decomposition Bi Urate is detected as minute elongated dumb-bells We have no proof that Uric Acid exists as a true Bi Urate. Solutions in normal urine. and if introduced into normal urine. they decompose. Nor have we any proof

that Bi Urates are found in healthy blood or interstitial juices Bi Urates though known to us as pathological products in gouty deposits are not strictly speaking known to us as pathological ~~products~~ constituents either of the blood or of the urine But Uric acid does exist normally in some form in solution in small quantities in healthy blood and in larger quantities in healthy urine Therefore the question rises What is the normal and physiological form of combination which is neither Neutral Urate nor Bi Urate ?

Amorphous Urate deposit examined

Amorphous Urates are not found chemically pure in urine Their most important reactions are masked by the urine In order to study them the deposit is filtered washed with rectified Spirit and dried Its most characteristic reaction viz its behaviour when heated with pure water may now be observed Some of the deposit be placed on a side under the microscope and distilled water insinuated under the cover-glass the amorphous urate is quickly disintegrated and lozenge shaped crystals of Uric Acid take its place This process continues till all the amorphous urate breaks down and disappears and its place is taken by Crystals of Uric Acid From this we learn that the amorphous urate is an unstable compound decomposing under the influence of pure water into Uric Acid and a soluble compound The same decomposition takes

place through more slowly in the urine and
" that is why crystals of Uric Acid are always formed
" in the amorphous sediment of urine which has stood
" for 24 hours". It is of much interest that the "urinary
excretion of Birds and Reptiles displays identically the
same reactions as the Amorphous Urates. When examined
in a fresh condition by the microscope it is found to
consist of minute spheres. about the size of White Blood
Corpuscles." exhibiting a radiated crystalline structure.
When treated in the same way as the amorphous
Urate deposit. the spheres are seen gradually to
melt away. with abundant emission of Colourless.
hexagonal tablets. of Uric Acid. The difference in
physical form between the two substances is a
mere accident of molecular aggregation, and the
one form can be converted into the other. the
difference being evidently due to the manner in
which they are cooled from their solutions.

This points to the probability that the amorphous
deposit in human urine. and the semi-solid
urinary excrement of Birds and Reptiles are
essentially one and the same substance.

Roberts next asks. "What is the constitution
of this substance.? Is it merely a mechanical mixture
of Ba Urate with varying quantities of free Uric Acid?
or is it a definite Chemical combination representative
of a new or 3rd order of Uric Acid salts. differing
essentially from the two regular orders. previously recognised?

Dr Bence Jones. published in the Journal

of the Chemical Society his researches on the Composition of the amorphous deposit of urates in healthy urine He shows that on adding pure water to the amorphous deposit after it has been previously washed with Spirit and filtered. That the part of the sediment not dissolved by the water is Uric Acid and the portion dissolved is pure Bi. Urate. On analysing some samples of amorphous urate to find out the proportion of Uric Acid to the quantity of base he found that the Uric Acid was in excess of the quantity required to form Bi Urates with the bases present. The separate analyses gave discordant proportions but their mean gave a proportion of Uric Acid which was very nearly twice as much as was required to form Bi Urates with the sum of the bases." This suggested to James that a third order of Uric Acid salts existed more Complex in constitution than the neutral and acid urates in which an atom of Bi Urate was loosely Combined with an additional atom of Uric Acid. "He therefore inferred that the amorphous urate deposit Consisted of or at least often Contained such a Combination." (Parkes Op cit p 11)

Quoted James sup. (Jour. Chem Soc. p209 Vol XV.).

" From these experiments it is evident that the amorphous " urinary sediment often contains much more Uric Acid " than is required to form Acid urates and that this " excess of Uric Acid is so feebly held in Combination " by the acid urates that washing with Cold water " will set free the crystals of Uric Acid. As no " Combination of this kind was previously known

" An attempt was made to form an artificial sediment
" of Urates which when washed with cold water - or boiled
" with water - would be decomposed into free Uric Acid & Urates.
(Uric Acid?)

Thomson 10.212. He says. "It appears from these experiments
that an artificial granular deposit may be formed
which is decomposed by washing with cold water
or by boiling into Uric Acid and acid urate of
Potassium. The granular substance may be considered
to resemble the Quadroxalate of Potassa which differs
from the acid oxalate by containing double the
amount of oxalic acid and following this nomenclature
it may be called the Quadrurate of Potassa."

Why the deposit should assume the
amorphous form is stated by Heintz (in Jour chem Soc. p 467 Vol XL.)
to be due to the fact that among the urates of which
the deposit consists, Urate of lime is present which
he shows is always precipitated as a fine amorphous
powder. He says. "(same page) that for the formation of this
finely powdery amorphous sediment Lime must be present
if Potassa is absent.

Pickards next states how he formed this amorphous
deposit artificially.

He dissolved Uric Acid in Potassium or Sodium ley.
Acidulated with Acetic or phosphoric Acid. till an
Acid reaction was obtained upon which a dense
white precipitate came down. When washed with
rectified Spirit dried and filtered. this was found
to possess the characteristic properties of amorphous
urate deposit. i.e. it was granular not crystalline

in appearance. under the microscope., decomposed by pure water. giving out an abundant formation of Uric Acid crystals. On analysis this Compound was found to consist of four equivalents of Uric Acid with one equivalent of Soda. He found that the portion which went into solution when the substance was treated with water. Corresponded. exactly. with the theoretical formula. of Potassium (or Sodium) Bi-Urate and that the Uric Acid that remained undissolved approximated in amount. to that which went into solution as Bi-Urate

The general formula for the Quadriurates as they may be termed would be $H_2(C_5H_2N_4O_3).MH.(C_5H_2N_4O_3)$. or more simply $H_2\bar{U}.MH\bar{U}$.

Dr Bence Jones' results did not come out quite accurately. in accordance with Theory. The quantity of Uric Acid dissolved out by water. should have equalled the quantity retained. in solution as Bi-Urate. Theory required the proportion 1:1. but the result obtained was 1·27 : 1. in one case. and 1·12 : 1 in another. It is difficult to say why he did not return to this study. unless it be as Roberts suggests. it was due to the difficulty of obtaining a sufficient supply of material for his experiments. A sufficient quantity can only be obtained by letting the urine stand for 24 hours. and by that time decomposition and the formation of Uric Acid crystals has commenced.

When Roberts took up and continued

Jones' Experiments the questions he had to decide were these. - Is the amorphous urate deposit together with the urinary excretion of Birds and Reptiles a true and definite Chemical Compound.? and does there exist a third order. of Uric Acid salts. differing essentially from the two urates. already known. and having a composition corresponding to the Hypothetical formula of a Quadriurate.?

In prosecuting this investigation he made use of the following materials.

(1) the amorphous urate deposit of human urine.
(2) the urinary excretion of Birds and Serpents both natural products
(3) Artificially prepared imitations of these natural products. made in the Laboratory.

Two lines of analysis were pursued.

(1) To estimate quantitatively the amounts of bases. and of Uric Acid in the samples
(2) To proceed by way of what may be termed Hydric Analysis. ie to decompose the substance with a large volume of water. and then to estimate respectively. the Amount of Uric Acid which was thrown out. in the free state. and the amount which went into solution as Biurate. If the Quadriurate theory be correct. these two amounts should be exactly equal.

But his difficulty. at the outset consisted in the fact. that his only sources of supply. - hospital wards and private patients. yielded material which on analysis gave results so inconstant in character. that no conclusion of any value. could be deduced

from them. The explanation of this lay in the fact that "Amorphous Urate as it exists in the urine exists under conditions of change which tend to progressively liberate the Uric Acid - and as the sediment had to be collected in separate portions from different urines on different days until a sufficient quantity had been gathered for analysis it is no wonder that gross variations in its Composition were observed". and that reliable results could not be obtained from materials procured in this way. He therefore devised the following means of obtaining a sufficient supply of the amorphous deposit.

He dissolved successive additions of Potassium or Sodium Bicarbonate in healthy urine till it became slightly alkaline. heating the mixture in a flask to 100° C. and shaking it up for a few minutes with excess of pure Uric Acid. By this means a large amount of Uric Acid was dissolved While still warm the mixture is thrown upon a filter and the filtrate Cooled under a tap of running water As the cooling proceeds a dense voluminous precipitate forms which is the exact Counterpart of the natural amorphous urate sediment. This sediment is removed by filtration washed with alcohol and dried at the temperature of the body." A much better result is obtained by dissolving 3 parts of Potas. Acet. in 100 parts of urine. On quickly Cooling the resulting precipitate has a finely granular character. just like that of the amorphous urine sediment

If cooled slowly at the Temperature of the room the precipitate fell in larger granules. or in "regular spheres. with a radiated crystalline structure, calling to remembrance the spheres formd in the urinary excretion of Birds and Reptiles".

This deposit was subjected to analysis by the water process. and yielded very constant results. When a portion of the dried deposit was stirred up in a beaker. with 1000 times its weight of distilled water. and slowly heated till near the boiling point. and left standing for 48 hours. when cool the liberated Uric acid fell out. in large crystals. The supernatant liquor was nearly all syphoned off. and the remainder with the deposited crystals. were thrown upon a weighed filter. The crystals were washed very sparingly with cold water. then with rectified Spirit. Then the filter was dried and weighed. This gave the weight of Uric Acid separated by water. The syphoned-off supernatant liquor. together with the washings from the filter were then heated to near the boiling point. strongly acidulated with H Cl. then set aside for 48 hours. The precipitated crystals were collected dried and weighed as in the preceding case. The amount of Uric acid by water was found to be. almost exactly equal to that retained in solution. as is shown in the two following simple experiments.

~~The first~~

results as in (19)

Table showing the results of Water Analysis of two samples of Amorphous Urate Sediment prepared by the Por Acet. method.

	1st Sample	2nd Sample
Uric Acid separated by water	0·080 grm	0·164 grm
Uric Acid dissolved as Bi Urate	0·077 grm	0·159 grm.

These results agree closely with the requirements of the Quadriurate theory.

Experiments were also made with the urine of Birds and an almost exactly similar result was obtained

Table III Water analysis of Fowls urine.

	1st sample	2nd sample
Uric acid separated by water.	0·160 grm	0·136 grm
Uric Acid dissolved as Bi Urate	0·165 grm	0·133 grm.

Similar results were obtained by experiments with the urine of Reptiles. In this case the water analysis process was not considered quite satisfactory on account of the difficulty in obtaining the secretion unaltered as it came from the Kidneys: being apt to be contaminated by the water used in cleaning the Cages in which the creatures are kept. From the following Table it will be seen that the urine of the Serpent when voided consists of Quadriurates mixed with a certain proportion of free Uric Acid

Table IV Water analysis of four samples of Serpents urine

Table IV

	1. grm	2. grm	3. grm	4. grm
Uric Acid separated by Water	0·138	0·110	0·204	0·215
Uric Acid dissolved as Bi Urate	0·117	0·085	0·141	0·140.

These discrepancies between the Calculated and obtained results however disappeared when a Comparatively pure specimen of the urine was obtained, and

subjected to quantitative analysis.

From these experiments it could also be deduced that the "Compounds of Uric Acid and Soda which constitutes the amorphous sediment. Contains exactly twice as much Uric Acid as the salt which is soluble in water".

With artificially prepared Quadriurate the details of whose preparation have already been given. the following results of analysis. both by the water-method and quantitatively were obtained.

(Ops cit p 25) Table VI. Water analysis and quantitative analysis of a sample of Potassium Quadriurate. prepared by the Acetate of Potash method. (1) Water analysis.

Uric. Acid separated by water 0·84 grm

Uric Acid dissolved as Bi Urate 0·85 "

Quantitative Analysis { Proportions per cent.

		Found	Calculated
Uric Acid	0·198 gram	89·75	89·60
Potassium	0·0226 "	10·25	10·40.

The numbers. in both these analyses of the Potassium Compound. Come out with almost perfect exactitude. in agreement with the Quadriurate theory of its composition These results were confirmed by the analysis of the corresponding Sodium Compound.

According to these researches. it is evident that the urine sediment which exactly resembles. the artificial Quadriurate. in appearance. Chemical relations &c. has also the same Chemical Composition and that this is also true of the Compounds of Uric Acid

in solution in the urine.

In the same way Rubel succeeded in preparing Quadriurate of Ammonium Calcium Magnesium.

He remarks with regard to the above experiments. (p 36.)
" The laws of analyses just detailed furnish an
" adequate proof that the Compound of Uric Acid
" which is decomposable by water is no mere mechanical
" mixture. but is a true and definite Chemical Combination.
" having a Centesimal Composition. Corresponding to
" that of a hypothetical Quadriurate with the general
" formula $H_2\bar{U}.M.H\bar{U}$. In deference to the authority
" of Bence Jones. I propose to adhere to the designation
" Quadriurate without however pre-judging
" whether in reality the analogy with Quadrosalute
" be a chemically sound one."

He explains the discrepancies between the results obtained by Scherer and Bence Jones. by proving that the amorphous deposit was apt to be contaminated with free Uric Acid or Biurate according as the solution from which it was precipitated was slightly to the acid or alkaline side of neutrality. He quotes the following experiment in proof of that contention (p 38)

" 500 CC. of an acid urine were divided into 2 equal portions. A and B. Sodium Bicarbonate was added to A. in the proportion of .1 %. The addition produced only a feeble degree of alkalescence
The urine was then heated to boiling and shaken up with one gram of Uric acid. After filtration it was

rapidly Cooled. under a running tap of cold water. The resulting precipitate was filtered off. washed with rectified Spirit and dried. This yielded to water analysis

	grm
Uric Acid separated by water.	0·164
Uric Acid dissolved as Bi Urate.	0·142.

The other portion B. was treated with Sodium Bicarbonate. in the proportion of 0·2% This addition rendered the urine freely alkaline. B was then treated exactly like A. The resulting precipitate gave with water analysis.

	grm
Uric Acid separated by water.	0·159
Uric Acid dissolved as Bi Urate	0·174.

In both cases. the precipitate when examined. under the microscope. was found to be wholly amorphous. That from A did not show any Crystals of Uric Acid and that from B. did not contain any Crystals of Bi Urate. These results are only explicable on the supposition that in the one case. the precipitate was contaminated with free Uric Acid. and in the other with Bi Urate in an amorphous Condition."

The Chemical Compounds of Uric Acid in the Blood and Urine.

The materials for a tenable theory. can be founded upon the researches of Horbaczewski and Roberts.

All pathologists agree that there is an excess of Uric Acid. in the blood in Gout.

Roberts tried to find out what were the conditions

this oxidation is not performed. or only imperfectly

This third possibility is proved untenable by the experiments of Horbaczewski who showed that Uric Acid. being formed in the body by increased cellular activity. is quickly excreted in the urine. There can be no increased oxidation because in diseases of the Heart and Lungs. in which oxidation is diminished. Von Jaksch showed that was no increased proportion of Uric Acid Haig (p 73) says "I noticed that in the blood of cases dying of Pneumonia (in which oxidation is deficient) there was generally a great excess of Uric Acid and 5 cases of this kind gave an average of '039 per cent."

(Ueber die klin. Bedeutung des Vorkommens von Harnsäure etc. im Blute pp 94-95.).

Von Jaksch (Ueber Uricacidaemie Deutsch Med Wochenschrift 1890 Aug. p 741). States the results of his examination of the quantity of Uric Acid in the blood of patients suffering from various diseases. He found it constantly present and in considerable quantity in 5 Cases of Pneumonia even during the febrile stage. In cases of Dyspnoea and Cyanosis. the more the blood is overloaded with Carbonic Acid. the more Uric Acid it contains. In Ueber die klinische Bedeutung des Vorkommens ~~de~~ von Harnsäure ~~im Blute~~ und Xanthinbasen im Blute 1891 p 96 he says. "Soviel geht jetzt schon aus den Beobachtungen hervor. Ueberladung des Blutes mit Kohlensäure die allmälig bei Herzfehlern bei Emphysem. rasch bei der Pneumonie auftritt, führt häufig zum Auftreten von Harnsäure im Blute. (The preceding sentence is a free rendering of this).

We deal now with (1) and (2)

(1) Increased production never produces Gout. So long as the Kidneys remain intact functionally.

(a) In Leucocythaemia e.g. in which we know there is a great preponderance of White Blood Cells in the blood. 3 to 4 grams of Uric Acid per day have been found in the urine by many competent observers. This over-excretion lasted a long time and must have been due to overproduction.

(b) The fact that though Uric Acid production is greatest in childhood and yet Gout (as long as the Kidneys continue normal in action) is a disease chiefly of middle age points also to the conclusion that Gout is not due to overproduction but to retention.

(c) An increase of Uric Acid in the blood during affections of the Kidneys of various kinds was found by Von Jaksch. (Op cit. p 742-3). In 12 cases of Kidney disease Uric acid was found in the blood of 9. of these 4 were cases of Acute nephritis, 1 of waxy degeneration and 2 of granular Kidney. (A similar list is given on p 97 of Ueber die Klinische Bedeutung etc). One of the 3 negative cases proves nothing as the amount of blood obtained was too small. The amount of Uric Acid was greatest in cases of atrophy of the Kidney and Uraemia.

(d) Many paludal beverages has been frequently noted by many writers as a cause of Gout, and the experiments of Prof Chittenden (above narrated) prove the same thing. This might be because alcohol by causing faster or inducing increased

tissue metabolism and thus liberating energy stored up in the body. enables a Patient to draw upon capital when he cannot upon income. Or it may be that the excessive use of alcohol or rather the excretion set by the kidney sets up a mild nephritis which interferes with the excreting powers of the Kidney.

(2) The same explanation may be given of the Gout of Lead poisoning in which the Kidneys are always found damaged. by an interstitial nephritis which results in atrophy. granular surface. and adherent Capsule. This is one of the best attested facts in Medicine. being witnessed to by many writers both English and French among whom. may be mentioned Charcot- Bucquoy. Jaccoud. Olliver. Garrod. . The latter states that one fourth of the cases he treated in Hospital for Gout were men whose occupation. brought them into close Contact with Lead. such as painters and plumbers. Garrod found Uric Acid in the blood of patients " affected with chronic lead poisoning even " when they showed no symptoms of Gout." " and he believed he could prove. " that the " quantity of Uric Acid excreted in the urine. could " be diminished by the administration of Lead " salts in the usual medicinal doses" (Lusion op cit p 73)

A comparison of the pathological anatomy of the Kidneys in Commencing gouty nephritis . and the early stages of Lead poisoning. makes it an

almost impossible task to distinguish the one condition from the other. apart from the history of the case. This consideration makes it extremely probable. that the early stages of Gout. even when there is no question of Lead poisoning. in the case depends upon an inflammatory affection of the Kidneys by which their capacity for the excretion of Uric Acid is lessened.

Sir Dyce Duckworth found among the forty patients 25 who exhibited symptoms of chronic Lead poisoning and one fourth suffered from chronic Nephritis. Note that at its beginning the Kidney disorder need give rise to very few anatomical changes as the primary cause is the decrease in the secretory power of the Kidneys by which Uric acid alone or in combination with other constituents of the urine. is less easily eliminated. The commencing incapacity of the Kidneys for excretion has been noted by Charcot who reports that certain odoriferous bodies. such as Turpentine cannot pass off in the urine. in early Gout.

We have now considered the second possibility - viz

(2) That Uric may be formed in normal quantity but fails to be excreted probably through defect in the Kidney

With regard to the above conception of the Pathogenesis of Gout we think that it requires further proof It has however the advantage over other Theories that it brings into one category all the etiological and pathogenetic factors with which we are

acquainted. and gives a plausible explanation of Gout both in poor and badly nourished subjects and the rich and bon-vivants. By it the enigmatical Gout of Lead poisoning is intelligible in the same way, as the other forms of Gout.

It may also enable us to establish a rational form of treatment instead of the old empirical methods. of therapeutics which often enough were directly opposed to each other.

The chemistry of Uratic precipitation in Gout.

Up to this point we have traced the history of the origin of Uric Acid in the fluids of the body We have shown that as the result of the experiments of Starbuczewski. it is formed in the body by the disintegration of the albuminoids substances of its tissues especially of the nuclein and that its excretion is increased or diminished by all the factors which induce quicker or slower disintegration of the cellular elements of the body. and especially. of the Leucocytes. That there is a temporary plus. Leucocytosis immediately after taking food. and especially flesh food. due most probably to the nuclein of the ingested food. We have shown also from the experiments of Von Jaksch. that Uric Acid exists in larger quantity in the blood of patients suffering from diseases in which there is great tissue change. and from diseases of the Kidney in which excretion is interfered with. Also we

have. shown from the experiments of Roberts. that the normal form. in which it appears in the urine is that of Quadriurates of Sodium Potassium. Calcium Magnesium &c.

Within the body it is formed as a Bi Urate in Gouty concretions and Tophi and we proceed now to Consider. the chemical and physical Conditions under which it is found within the body. We have seen that Uric Acid is a normal product of the active metabolism. continually going on in the body. and that it is excreted by the Kidneys. That if under any circumstances there is increased production. or decreased elimination it accumulates in the tissues. and manifests its presence in various pathological processes. The most Characteristic way in which it does so. is as chalk-like deposits in and around joints. or as chalky nodules in different parts. In these positions it appears under the microscope as delicate crystals aggregated as bundles. star forms. or clusters. and Gouty phenomena are due to their presence. in fact they are foreign bodies

If they could be kept in solution Gouty phenomena would not exist. unless of Course. the toxic theory of its action. upon nerve and muscle tissue can be shown to be true.

When we reach this stage of our enquiry. certain questions necessarily suggest themselves to us. Some seem capable of being answered. others not

Does the Uric Acid exist as such in solution in the blood plasma or is it in combination with some other body? How does the Bi Urate (formed in Tophi and Gouty joints) originate from the nascent Uric Acid? What are the conditions that determine its solubility in the blood, lymph, and synovia and What are the factors which determine its precipitation or tend to prevent its precipitation?

We have quoted the evidence already by which Roberts shows that the normal or physiological Condition of Uric Acid in the body is that of a Quadriurate and that any departure from this Condition must be regarded as pathological.

We shall later quote his experiments which show that Quadriurate in the urine breaks up into free Uric acid (known as Gravel) and Urinary Sediment. We now propose to show from his experiments the converse changes which the Quadriurate undergoes in the blood and lymph and which lead up to the formation and deposition of Sodium Bi Urate in the tissues.

Theory of Urate precipitation

We examine first the solubility of Gouty Concretions ie of Sodium Bi Urate in various media, such as Serum Synovia and various saline Solutions Then we examine and compare the behaviour of free Uric Acid in the same media.

Sodium Biurate in water.

(a) In water at blood-heat Roberts determined that Sodium Biurate was soluble in the proportion of 1 part in 1000. and used this as a standard for comparing the solvent power of other media.

(b) In Serum Sodium Biurate was found to be soluble in the proportion of one part in 10,000 ~~and~~ The following experiment is very instructive A metatarsal bone of a gouty subject encrusted on its articulating surface with chalky matter was suspended in blood serum. Twelve months passed before there was any evidence that the deposit was being dissolved When suspended in distilled water another metatarsal of the same subject, similarly encrusted had its whole deposit dissolved out in a few days.

(c) In Synovia. This behaved exactly in the same way as Serum. only minute traces went into solution. The cause of this inability of Blood Serum and Synovia to dissolve Uric Acid and its Compounds was shown by experiment to be dependant on their saline ingredients and in no way upon their albuminous Constituents. Serum deprived of its salts dissolved Uric Acid and its compounds as completely as distilled water had done.

Serum and its derivatives Lymph and Synovia though differing from each other in their albuminous elements are almost identical as regards their saline Constituents both as to

quantity and quality. and of these Sodium salts largely preponderate. This can be seen by an inspection of the following table

Table (Roberts op cit p 75) showing the per centage of the several salts in blood-serum.

Sodium Chloride	·50 per cent	Sodium Salts = ·73 per cent
Sodium Bicarbonate	·20 " "	
Sodium Phosphate	·03 " "	
Potassium Salts	·06 " "	All other salts ·11 " "
Calcium Salts	·05 " "	
Magnesium Salts		

This suggested to Roberts to study after the method adopted by Bence Jones - the chemistry of urate precipitation by means of an artificial solution imitating closely the composition of Serum as regards its salines. A glance at the above table shows that the saline basis of Serum consists of Sodium Bicarbonate and Sodium Chloride so largely do they preponderate. Roberts found experimentally that a solution composed of the above salts in the proportion shown in the table." reacted with Uric Acid and the urates in the same manner as Blood Serum itself He called this the standard Solvent or standard solution and with it he subjected Uric Acid and the urates to the same tests of solubility experimentally as he had done with blood-serum. He varied in many ways the conditions of Temperature and Time, and varying modifications

of the Constitution of the standard Solvent. and found they behaved exactly. as with serum. Only the smallest traces. of Bi Urate were taken up by it at 100° F. As saline substances are very largely employed. in the treatment of Gout, the value of such determinations of their effects on the solubility of Urates. is obvious.

Sodium. The Bicarbonate. Chloride. Sulphate. Phosphate and Salicylate all diminished the solvent power of the medium. (ie hastened precipitation.) and the alkalescence or neutrality had not the slightest influence on the result.

Potassium. Salts. exercised no influence. neither for nor against the solubility of the Bi Urate.

Calcium Magnesium and Ammonium salts. diminished the Solvent power. of the medium on Bi Urate.

Summary of the Results obtained by Roberts. (p 82).

(a) The influence of a salt depends exclusively. on the nature of the base. and has no reference to the Acid radicle. with which the base is Combined

(b) Salts with an alKaline reaction. such as Carbonates and Phosphates. do not differ in the least from neutral reacting salts such as Chlorides & Sulphates.

(c) The salts of Sodium exercise a strong. deterrent influence. and the deterrent influence increases

with the increasing per centage of the salts in solution. Salts of Calcium Magnesium and Ammonium have also a deterrent effect, but slighter than the salts of Sodium

Behaviour of Uric Acid with blood-serum and with the Standard solvent and with synovia.

This introduces us to a very important part of the enquiry. We know that Uric Acid exists in the blood it can be demonstrated experimentally to be there. We know its mode of origin (so far as this enquiry is concerned). but we do not know by what means it comes into solution in the blood or the factors which control its precipitation in the body.

When Sodium Bi Urate is brought into contact with blood-serum Synovia or the standard solvent. it simply passes into solution, and is taken up by these fluids. unchanged. and the quantity which passes into solution is dependant on the salts contained in the fluid. But free Uric Acid in contact with these fluids on the other hand does more than simply dissolve. It passes through a series of Chemical changes. It first combines with the bases in the medium then passes into solution and after some time is precipitated as Bi Urate.

When Uric acid is digested with serum - synovial or the standard solution. at about 100° F. and frequently shaken up. it will be found that a considerable quantity. passes into solution to the extent of 1 in 5000.

The. solvent. power of these media depends upon the presence in them of Sodium Bicarbonate. and not at all on the Sodium Chloride. which has no solvent influence on the Uric Acid: A solution of Sodium Bicarbonate alone. has as much solvent power. on Uric Acid as when it is a constituent of these media along with Sodium Chloride. The question now arises. What is the Combination in which Uric acid enters into solution.? It Cannot be Bi Urate. for it is almost insoluble. in these media. . Nor Neutral Urate. for it cannot exist in the presence of the Carbonates.

There is only one conjecture left. viz that it Comes into Solution as a Quadri urate. But we must have more Solid ground to stand on. than mere conjecture.

If Uric Acid were dissolved in standard Solvent. and evaporated to dryness. the resultant residue was always. a Bi Urate. The reason being that as evaporation proceeded. the solution gradually became more rich. in Base (Sod & Carb^{te}) and therefore more potent to change. Quadri urate. (assuming for the present what we shall afterwards demonstrate).

into Bi Urate. Roberts made many attempts to throw down a Quadriurate from the solution but always failed till he took advantage of the different solubility of Quadriurate at different temperatures By the following experiment (op cit p85) he succeeded in proving that Uric Acid passes into solution in the presence of alkaline Carbonates as a Quadriurate

" Uric Acid in excess was digested at blood
" heat* in a one per cent solution of Sodium Bicarb+
" under constant agitation for 20 minutes. The filtered
" product was rapidly cooled on ice. It then threw down
" a Copious* Amorphous deposit, which when duly
" washed on the filter with rectified spirit to free it
" from adherent Carbonate gave the characteristic
" reaction of Quadri-urate, that is to say it was decomposed
" by water with abundant emission of Uric Acid crystals
" A corresponding* experiment with a .5% solution of
" Pot-assium Bicarbonate yielded exactly the same results.
" From the above experiment it is evident that
" when Uric Acid comes into Contact with blood serum
" or standard solvent it enters into solution in the first
" instance as a Quadriurate But the process does
" not stop here. The Quadriurate gradually takes
" up additional atom of Urea and is thereby converted into
" Bi Urate" which is by degrees precipitated in the

Crystalline form. This may be seen from the following experiments.

Experiment with the Standard Solvent.

" A gram of Uric Acid was introduced into
" a flask with 200 cc of the standard solvent. The flask
" was tightly corked and placed in the warm chamber.
" where the temperature was continuously maintained
" at 100° F. A considerable amount of Uric Acid went
" into solution, but a portion remained undissolved.
" at the bottom of the flask, leaving a clear supernatant
" liquour. Things remained apparently unchanged
" until the evening of the second day, when a few
" stars of Bi Urate were detected among the undissolved
" sediment of Uric Acid. On the third day however a
" rapid change was observed to be taking place.
" Consisting in an abundant precipitation of stars
" and tufts and detached needles of Bi Urate.
" On the fourth day the precipitation appeared to be
" nearly complete for the supernatant liquour now
" showed only small traces of Uric Acid when it was
" treated with Hydrochloric Acid."

An exactly similar result was got by dissolving Uric Acid in the Serum of the blood of the pig.

In a third experiment with the standard Solvent the conditions were varied by decanting off the supernatant liquid from the Uric Acid

Still undissolved. It was placed in a corked phial in the warm chamber. It remained undisturbed for two days. On the third day it began to precipitate and on the fourth day a copious deposition of crystalline Bi Urate took place. On the fifth day the process was completed. and the supernatant liquour was found. on acidulation to contain only traces of Uric Acid.

Roberts says with regard to the above experiments. "It was impossible not to be struck with a certain rough resemblance between the results observed in these experiments. and the phenomena of the Gouty paroxysm. In the Gouty subject it is assumed. that the blood becomes more and more impregnated. with Uric Acid until. after a certain period of incubation. has been accomplished. sudden precipitation of Sodium Bi Urate. takes place in and about the joints and the 'fit of the Gout' is declared. Then follows a process of recovery. with restoration of the blood to a purer state. that is - with a lessened impregnation of Uric Acid. In the artificial counterfeit we observe a similar succession of successive events firstly. impregnation of the medium with Sodium Quadriurate. - secondly a period of incubation or maturation - during which the Quadriurate passes.

" with Bi Urate. Thirdly somewhat sudden precipitation
" of Sodium Bi Urate in the crystalline form. and lastly
" restoration of the medium to Comparative purity"

Reaction of Uric Acid with Synovia.

It is a matter of Common observation. that uratic deposits choose as their seat of election for deposit situations in and near joints. and a very natural Question which arises is Why? Can the synovia have anything to do with this. It was not easy to submit this question to the arbitrament of experiment. on account of the difficulty of obtaining sufficient quantity of Synovia to experiment with. Roberts however succeeded on two occasions in obtaining a supply with which - and also with serum from blood of the same ox. he experimented He found that "when these media were impregnated with Uric Acid to an equal degree. precipitation of Bi Urate began distinctly a little earlier. in the Synovia. than in the Serum. Though these experiments are not Conclusive. they at any rate suggest. that probably the Key to the preference. of Uratic deposit in and near joints lies in some difference in the Composition of these two fluids. such as that synovia may be more largely charged. with Sodium salts than the Serum from which it is derived.

Gelatinous or hydrated modifications of the Urates

Gelatinous modifications of the Urates differing from the granular and crystalline forms. were first observed by Dr Ord. in the course of his researches "on the influence of colloids. upon crystalline form and cohesion" It is of great interest in the present enquiry. to know as much as possible about the modifications in the constitution and form of the Urates because. such gelatinous forms may form an intermediate Step in the series of changes. by. which Uric Acid becomes. deposited in the tissues.

Dr Haig mentions this gelatinous form (op cit p 388). as one of the alternative explanations of the way in which. Uric Acid acts in the body. to produce increased blood pressure. which he observes whenever he finds excess of Uric Acid in the blood. According to him Uric Acid may act like Digitalis or Erythrophlaeum. locally. on the Blood-vessels. and raise the blood-pressure. (1) by contracting the muscular tissue of their walls. or (2). it may act directly on. and through the Vaso-Motor centre. or (3). it may act by mechanically. obstructing the Capillaries. He puts forth ~~accepts~~ this theory as. a probable explanation of the phenomena of Raynaud's disease and in Purpura. He says. "if the vessels

of the superficial parts. such as the skin are obstructed by. (Colloid) Uric Acid. so that the surface temperature is reduced. and even the nutrition of the skin. is eventually affected. It is probable that in these Capillary vessels. where. the circulation is absolutely at a stand. the very walls of the vessels themselves will suffer in their nutrition. and deteriorate, so that even when the blood again passes. into them they may bulge and leak. and thus small extravasations of blood. result." He thinks this hypothesis may explain the way. in which Purpura is linked on. to other Uric Acid diseases. as the Rheumatic group. and also to Chronic Bright. - Dyspepsia Post-febrile Conditions and Menstruation. He also thinks Thrombosis. (op cit p389). may in some cases be explained. by this Colloid form. passing from the arterial to the Venous. system. and forming the nucleus of a Thrombus. - Roberts (in this connection). thinks it Conceivable. that needles of Ba Urate - while Quadriurate is passing. into the Ba Urate Condition in the blood. "might Constitute. foci round which Clotting might take place. and that the Thrombosis not infrequently observed. in Gouty cases. might thus be accounted for (p98).

Roberts is of opinion that the gelatinous.

forms of Uric Acid is not a true colloid. because it passes with ease. and unchanged. through a dialyser - but that it is a hydrated form. just as the crystalline Ba Urates. are an anhydrous form.

Formation of the gelatinous form of Uric Acid

This gelatinous form. may be formed from the Quadriurate as follows.

A 5% solution of Soda Phosphate. is heated to boiling with excess of Uric Acid - filter hot - on cooling - the filtrate sets into a jelly. This jelly possesses. the characteristic reaction of a Quadriurate. ie. it is rapidly decomposed by water. with a copious emission of Uric Acid crystals. When the passage of the urates into this gelatinous form. is observed taking place under the microscope. it appears sometimes as amorphous matter. and sometimes as. "beautiful soft. transluscent spheres". and. According to Roberts. the urinary excretions of Birds and Reptiles. may be first voided in this soft translucent condition, and gradually gain their radiated structure. as they pass through the lower urinary passages. There would certainly be an advantage. to the delicate cast tubules of the Kidney that the excretion should assume this soft.

gelatinous globules form in passing through them.

Summary of the history of Uric Acid in the Body (a) in the normal state. (b) in the gouty state.

"The above facts enable us to obtain a coherent view of the state and destiny of Uric Acid in the body. It has been shown that in normal urine Uric acid always exists as a Quadriurate, and that in animals which eliminate their nitrogen as Uric Acid like birds and serpents. the urinary secretion is composed entirely of the same combination. Proof has also been furnished that in media containing alkaline carbonates. such as the serum of the blood, and its derivatives lymph and Synovia. Uric Acid passes into solution. in the first instance as a Quadriurate. From these Considerations. it may be inferred that in the normal state Uric Acid is primarily taken up in the system as a Quadriurate. that it circulates in the blood as a Quadriurate. In perfect health the elimination of the Quadriurate proceeds with sufficient speed and completeness to prevent any undue detention. or any accumulation of it in the blood. But in the Gouty state, this tranquil process is interrupted

either from defective action of the kidneys. or from excessive introduction of the Urates. into the circulation. and the Quadriurate lingers unduly in the blood and accumulates therein. The detained Quadriurate circulating in a medium which is rich in Sodium Carbonate. gradually takes up an additional atom of base. and is thereby transformed. into Bi Urate This transformation alters the physiological problem The Uric Acid or rather a portion of it. circulates no longer as the more soluble and presumably. easily secreted Quadriurate but as Bi. Urate which is less soluble and probably also — (either for that reason. or because it is a compound. foreign to the normal economy.) less easy of removal. by the Kidneys. The Bi Urate thus produced exists at first. in the hydrated or gelatinous modification - But with the lapse of time. and increasing accumulation. it passes on into the almost insoluble anhydrous. or crystalline condition and then precipitation of it becomes imminent or actually takes place" (Roberts op cit p 94)

We next proceed. to enquire what are the conditions which hasten or delay. the processes which culminate in the precipitation of Sod min Bi Urate.

If the processes which we have seen

going on in the experiments above detailed. with regard to the solution and precipitation of Sodium Bi Urate. and Uric Acid. in Blood. Serum and Synovia. and the standard solvent. represent with any degree of truth. the processes which go on in the body. and culminate in the precipitation of Uric Acid. It would further be of much interest to know what are the causes. which determine precipitation of Bi Urate in the tissues

We have seen that these processes. consist of three distinct chemical changes.

(1) Uric Acid comes into solution as Quadriurate. and is converted into the hydrated Bi Urate.

(2) The hydrated Bi Urate is changed into the anhydrous Bi Urate,

(3) The anhydrous is changed. into the crystalline form

For the sake of brevity Roberts sums up these 3 processes. under the Name Maturation.

We next enquires what effects on this process were produced by Temperature. Percentage of Uric Acid in solution. and the addition of various saline and other substances. to the medium

(a) Temperature. Maturation was completed more quickly. at a Temperature of 100° F. than at the Temperature of the room. (about 65°). though the ultimate result was the same.

(7) Quantity of Uric Acid in solution

No factor exercised more influence on the rate of maturation and the abundance of the precipitate than this factor as will be seen from the following table. (page 7).

Table XV Showing the influence of percentage of Uric Acid in the medium on the speed of maturation and the time of advent of precipitation

Quantity of Uric Acid Contained in the serum	Time of precipitation of Sod^{m} Bi Urate.
1 in 1000.	Precipitation began in 6 hours. copious pp^{n} in 14 hours.
1 " 2000	Precipit^{n} began in 33 ho. Copious pp^{n} in 3 days.
1 " 3000.	Slight precipit^{n} began in 3 days. more copious in 12 days.
1 " 4000.	A few needles of Bi Urate on 6th day: more needles & tufts in 12 days.
1 " 5000	A few short needles on 13th day. In 30 days needles more numerous
1 " 6000.	No needles. discoverable in 14 days. A few detected in 40 days.
1 " 8000.	No needles. could be detected after the lapse of 40 days.

In the inflammatory joint attacks in Gout are produced by the deposition in the cartilages of the joints or of the fibrous tissues around joints of such needles and clubs. Such deposition can only take place when the fluids bathing these structures are impregnated with Uric Acid in the proportion of 1 in 2500. At the proportion of 1 in 5000. the deposited needles were about the length of a Red Blood Corpuscle or almost 2 or 3 times as long. and Roberts suggests that the precipitation of a shower of such needles in various organs might

account for certain irritations which characterize irregular Gout. and even as has been already noted might constitute foci around which clotting might take place and thus account for the Thrombosis often associated with Gout. That such conditions are possible may be learned from Garrods observations. for he obtained by quantitative analysis from the blood-serum of one of his Patients Uric Acid in the proportion of 1 in 5740.

Influence of Salines on Maturation.

This was investigated by adding small quantities of various salts to Serum impregnated with Uric Acid. and observing whether these additions accelerated. or retarded precipitation The beginning of precipitation was observed at 2 points

(1) At its very outset. when needles of Bi Urate were revealed by the Microscope.
(2) When precipitation became more copious, and was recognised by the naked eye.

(a) Soda Salts I found that in Serum rich in Soda salts. Bi Urate crystals were more easily separated and that the salts with alkaline reaction. the Carbonate and phosphate. were as efficient in producing precipitation as the Chloride and sulphate. whose reaction is Neutral.

I found that a solution of one part of Uric Acid. in 1000. of Serum. deposited microscopic crystals at the end of 6 hours. and a copious precipitation in 16 hours.

and that the less the per-centage of Sodium salts in the serum. the precipitation was proportionately postponed-

(b) Potassium Salts All salts of Potash irrespective of their acid radicle. retard precipitation of crystals of Bi Urate. Potass Iodide and Bromide. act in this respect like the Carbonates. and phosphates. The reaction of the Potash salts was. as in the Case of the Sodium salt. a matter of indifference

(c) Calcium and Magnesium Salts of Lime and Magnesia show no decided action, although they appear to slightly delay precipitation.

(d) Lithia salts and Pyuazine. in the proportion of .1 to .2 per cent. do not really affect. the rapidity and degree of precipitation.

Place of Uratic Precipitation

Crystals of Bi Urate are not precipitated in all the tissues of the body. indifferently. They seem to have an elective affinity. for tissues belonging to the Connective tissue Class. such as. Cartilage Ligament. Tendon. Skin and subcutaneous tissue - and these tissues are not equally liable throughout the body. On the other hand certain other tissues enjoy a complete immunity from Uratic deposits. viz. Muscle Brain. Liver. Spleen Lungs.

There seems to be another election in action among these tissues. of the Connective tissue class. Viz- those Cartilages Ligaments, and Tendons. which are bathed with Synovia. are more liable to become infiltrated. with Urates. Then too when these tissues are placed more superficially. and in the Cooler parts of the body. as in the extremities they are more liable to deposition. than when situated in the deeper and warmer parts of the body.

Similar elective affinity for precipitation in certain tissues in the case of Jaundice

It is worthy of notice in this Connection. that in the poisoning of Jaundice Certain tissues exercise a selective action upon the bile pigment. and by fixing it in their substance. so protect other and more vital tissues. Bouchard in his "Auto-intoxication" p 229. says "I have showed that there are two poisons in the bile. the biliary salts which have always been recognised as poisons. and a substance which up to the present has not been appreciated from a toxic point of view. viz the colouring matter. This is I think a new revelation in pathology. I wish also to call attention to the fact, that although in Jaundice a considerable quantity of poison enters into the system Nevertheless in the majority of cases. the introduction of poison is not followed by death. as the organism

is doubly protected. In the first case the Kidneys carry off part of the pigment. and the biliary acids and their derivatives. Therefore the urine becomes poisonous ---- the fibres of the Connective tissue fix the most important of the poisons of the bile. the colouring matter. The tissues by becoming coloured withdraw from the circulation in increasing proportion. This poison and exercise gradually a condensing power ---- the white fibres of the Connective tissue by fixing the bilirubin. protect the Nerve Cells. Thus the tissues serve to protect the organism against certain poisons. Experience shows us that the most intense form of Jaundice. viz Black Jaundice. does not kill. precisely because the colouring matter which is ten times more poisonous than the biliary salts becomes fixed (p 227.)."

The reason why the tissues exercise this selective action is because of their chemical Composition The tissues rich in Soda being earlier attacked. than those which contain less Soda. There is the greatest tendency to precipitation. when the following two factors preponderate. viz high percentage of Urates in solution and tissues rich in Soda Salts

Roberts gives the following Table of the proportion of Sodium salts in the various tissues (p 103).

Table. Showing the per-centage of Sodium Salts in the several Fluids. Tissues, and Organs of the Body.

Blood Serum	·70 per cent	Blood Corpuscles.	·20 per cent.
Lymph	·70 " "	Brain	·20 " "
Synovia	·80 " "	Muscle	·08 " "
Cartilage.	·90 " "	Spleen	·04 " "
Fibrous tissue	·70 " "	Liver	·02 " "

He says. "From the above Table it can be seen. that Brain has only one fourth. the per centage of these salts. as compared with Cartilage. and fibrous tissue. and muscle only one tenth. This means that Brain has. 4 times more power of dissolving, and Muscle 10 times more power. of dissolving Sodium Bi Urate. than Cartilage and fibrous tissue. And therefore respectively 4 and 10 times more power. of resisting its precipitation in their substance" (p104).

And just as in the case quoted above from Bouchard. fibrous tissues protect the more vital tissues, Cartilage and fibrous tissues by their "preferency" to induce uratic precipitation - protect the more vital organs. of Gouty patients from such precipitation where they would produce more deadly effects.

Influence of Synovia — From a glance at the above table it is not difficult. to understand why Synovia is so

intimately concerned in the development of Gouty phenomena.

(1) It contains more salts of soda. than its congeners.

Serum and lymph. In many cases it has been found heavily laden with. Crystals of Sodium Bi Urate.

(2) It is usually found. in an enclosed sac or cavity in which it has little opportunity for movement or renovation " Blood and lymph being more Continuously and more rapidly in motion. Cannot deposit many crystals. in every situation, but when Synovia is saturated with Uric Acid. it can rid itself of the excess. by depositing Bi Urate Crystals. in the joint cavity. In the slighter forms of Gout. the disease is limited to. single joints. and to the surfaces of the Cartilages. and the tendons with which the synovia comes in contact. The Cartilage appears to become impregnated. with the synovia in a purely mechanical manner. Sections of the Cartilage are examined under the microscope. it is seen that the deposit lines the synovial surface. of the cartilage. and that it becomes progressively sparser. towards the deeper layers. the central and deepest parts being often quite free from deposit."

Roberts suspended the metatarsal bone of a pig in a flask of warm Concentrated solution of Sodium Bi Urate. and after adding a few drops

of chloroform. to keep the solution aseptic. left it standing at the ordinary room temperature As soon as the solution cooled. the P_2 Urate gradually fell down and after some time he found that the cartilage of the bone suspended in the fluid. was infiltrated with crystals which. just as in Gout. were chiefly laid on the surface of the cartilage and became less frequent toward the deeper parts.

Want of space forbids us. discussing the question why certain joints are more apt to have deposits in them than others. And also. the anomalous appearances of Gouty joints at an autopsy showing no sign of deposit. and the Common phenomenon of. deposits found in joints with no history of gouty attacks. We next proceed to enquire.

How does Uric Acid produce its injurious effects.?

Two possibilities suggest themselves

(1) Uric Acid and its Compounds. act as a poison

(2) Mechanically.

(a) Its a Poison (1). There is no proof that this is so. unless Haigs theory. already explained (ante). be accepted as showing a toxic property in Uric Acid. In fact any experimental proof that exists points quite

in the opposite direction. Experiments by Bouchard ("Auto-intoxication pp 51. 52. 118) prove that intravenous injections of Uric Acid in much larger per-centage than ever it is found in the human body not only do not Kill but do not even seem to be toxic.

He says (p51). "The Gouty man can have hundreds of grammes of Urates in his deposits without being intoxicated by it. Besides I have been able to inject experimentally into the blood. 20 Centigrammes of Uric Acid. for each Kilogramme of animal. without apparent accident. - I have even been able to inject as much as 64 Centigrammes of Uric Acid in solution in 160 cc of water. to which the necessary additional quantity of Soda had been added to produce its solution (then follow details of the experiment)

Uric Acid cannot be proved to be toxic in any quantity in which it is found possible to inject it in any quantity of water. by which it can be held in solution, for it can be shown that the same quantity of water. will Kill the animal. - - - I add we can never introduce into the veins of an animal more Uric Acid than in the first experiment since this dose of Uric Acid would saturate a quantity of water which optimally is toxic

(2) By analogy. Uric Acid is not poisonous because its physiological homologue. Urea is not poisonous, Each forms in its separate domain. The final term of nitrogenous metabolism. Urea has been shown by Bouchard. and so also has Uric acid (supra). he says. (261) "Urea are few bodies in the organism so perfectly fixed as urea. if we except albumin and the water which naturally exists in the blood." and again p267 "we are thus led to this unexpected conclusion that the substance Urea. which has been for such a long time. the resource of physicians. is especially injurious when it is deficient".

(3) As a matter of fact the fluids in the tissues of a gouty patient. are charged to saturation point with Ur Urate. immediately before an outbreak for of course no precipitation can take place, till this point is reached. - yet not only are there no toxic phenomena. experienced. but as D Haig shows. the patient has an unusual sense of well being. so much so that those who have had many attacks. have come to regard this sense of bien-être as the warning precursor of an attack.

(b) Mechanical "The manifestations of irregular gout are so extremely diverse. in seat and character. that it is hard to believe that they can be

produced by one and the same toxic agent.
Sometimes they implicate the Stomach, sometimes
the Liver, Heart. Lungs. and oftenest of all the
Nervous System. It is much easier to explain
these phenomena by imagining that a series of
events takes place. in the fluids bathing the tissues
similar to what we saw taking place in vitro
in the above-cited experiments of Roberts. and
especially when we remember the deposition of microscopic
needle-shaped. ~~Crystals~~ varying in length from
one to three Red. Blood. cells.. If anything similar takes
place, ~~in~~ an actual precipitation of microscopic
Crystals of Bi Urate. in the Connective and fibrous
tissues. or into the fibrous tissues of Nerves. which
Control the functions of tissues and organs, then these
irregular gouty phenomena. are explainable simply.
as an irritation mechanically produced. or
we may imagine the Bi Urate Crystals falling.
"in sudden and copious showers". Causing
sharp inflammatory reaction. a regular arthritic
seizures. Or again they may fall. in "gentle
sprinklings sufficient to cause irritation". or
they may simply act as a foreign body.
obstructing the lymph channels. and giving
rise to Thrombosis.

Sir W Roberts thinks if these slighter precipitations "instead of falling on the joints. fall upon the membranes of the Brain or upon the fibrous sheaths of the Nerve roots. they would yield I submit an adequate explanation of the phenomena of irregular gout". He suggests that such precipitations would be very difficult to find. "when the stress of saturation of the fluids. with urates was relaxed. and the blood again recovered its power of dissolving these compounds., these slight deposits would be speedily removed by re-solution. and not a trace of them be found at an autopsy."

But such precipitations of Bi Urate. have been found and recorded. many times. Lewson says (Op cit p82) "Watson. Gairdner and Dufau. report the finding of Bi Urate deposit upon the meninges". Cornil found microscopic crystals of Bi. Urate. in Cerebro-Spinal fluid. Albert has seen uratic Concretions. on the spinal meninges. Ollivier found at the autopsy of a gouty subject. who had been troubled with a feeling of Constriction in the throat. chest and abdomen. as well as lancinating pain in the extremities, deposits of Bi Urate. on the spinal dura-mater. from the 3rd Cervical vertebra. to the sacrum extending for some distance

along, and compressing the roots of the spinal nerves.
Fuchsin Schroeder Van der Kolk. (Le Cerveau traité du Medecine Paris 1891 Tome 3 p. 492). has seen aggregations of Bi Urate Crystals in the Neurolemma of peripheral nerves.

Indeed there is quite a plethora of evidence of Uratic deposits in various organs and tissues of the body. Garrod observed them in the cartilages. (See ut supra) Virchow in the right vocal Cord. (Archiv Vol 44) Litten on the crico-arytenoid ligaments and joints. (Virchow Archiv. 62 p 132 quoted by Duckworth). -
Lecorché has described Uratic Centaning Uratic deposits and Duckworth notes the same - as having observed by Dr Moore (Irish Hosp Gazette. July 1863.). Indeed if need be pages could be filled with evidence from Competent observers of Uratic deposits in the joints bronchi. cardiac. heart and its valves. pericardial effusion (Garrod). Kidney; meninges, muscle, nerves, pharynx, veins; villi. (Huyem. quoted by Ewart p 132).

There can be no doubt but that such precipitation is often very imminent. And it is not difficult to realise this when we keep in mind the facts and experiments stated above. and that the blood is supersaturated at 1 in 6000. and that such proportion of urate has actually been found.

by. Sir A Garrod. in the Serum of a Gouty man
Roberts while admitting that this explanation
rests. on no surer. basis than that of a "strong basis
of à priori probability". thus sums up his views
(Loc. cit p 115). "Uric Acid and its Compounds
are deleterious simply. because of their sparing
solubility. in the bodily media. It may be said
that the Cause of Uric Acid Gravel. is the sparing
solubility of free Uric Acid. in the urine, and in
like manner. it may be said that the final
Cause of gouty precipitation is the sparing solubility
of sodium Bi Urate in blood Serum. lymph
and synovia.

Indications for treatment. as suggested by the present inquiry. leaving out such treatment as is suggested by clinical experience.

In order that treatment of any aberration
from a normal physiological process. may be successful.
it is essential that it be rational, that is founded
upon a true and adequate. Conception. both of the
physiology. and pathology. of the organs. whose departure
from physiological righteousness, is the Cause of the
suffering. we are called upon to treat. We therefore
Consider treatment in the light of these researches we

have been studying.

According to these views Uric Acid originates from the breaking down of the nuclei of cellular tissue whether that be cellular tissue introduced as food or cell-waste induced by normal and physiological work or cell-waste induced by pathological processes. So long as the Kidneys remain functionally intact this plus Uric Acid can be excreted but whenever by plus formation or introduction or minus excretion the Uric Acid accumulates in the blood and is precipitated as crystalline Bi Urate in the tissues all those phenomena which we summarise under the name Gout arise.

Our treatment will therefore be guided by first our knowledge of the origin of Uric Acid and second those chemical processes involved in the precipitation of Uric Acid as Sodium Bi Urate in the tissues.

Before proceeding further we might glance for a few minutes at an extremely interesting theory propounded by Sir W. Roberts (Op cit p 21) by which he thinks "Uric Acid in the mammals urine should be regarded as a "Mockery" of some ancestral form which eliminated its nitrogen as Uric Acid. Ammonium Urate is the physiological homologue of the entire renal activity of birds and serpents in whom the renal function

is presented to us. in its primitive simplicity. In these creatures the Kidneys perform one single and simple physiological act. namely. the elimination of nitrogen as Uric Acid. --- In regard to the purine function of the Kidney. Nature solved the problem easily. by substituting Urea for Uric Acid. But why was not the problem solved Completely. Why was there left in mammalian urine. this small and apparently purposeless, but. to man, very mischievous residuum of Uric Acid.? No satisfactory answer. Can at present be given to this question. It seems not impossible that the explanation lies. in the fact that the mammalian type. the most recently evolved. of the vertebrate types. has not - yet - in this particular. reached its ideal perfection".

We consider treatment under the heads of (1) Prophylaxis (2) Medicine.

Prophylaxis. (a) Heredity.

No fact is more surely established in connection with our Study. than the influence of Heredity. and though we cannot alter a man's heredity. yet the knowledge that a patient is descended from a Uric Acid stock. enables us to make use of precautionary and prophylactic measures.

b Diet. Remembering our Conception of the origin of the

peccant material. The most obvious precaution we can take is. to lessen its introduction Therefore we consider what changes if any. should be made in a Patients diet. So long as Uric Acid was considered to arise from the disintegration of the albuminous Constituents of food. it was natural to limit as far as possible the Consumption of nitrogenous articles of diet. Rubini recommends. Considerable reduction of the nitrogenous elements of food. He says (op cit p122) "The chief point of Therapeutic interest that has clearly been made out, is this - that the ingestion of large quantities of proteid matter. is attended with an increased production of Uric Acid and vice versa. It does not appear clear that proteid substances derived from the animal Kingdom differ in this respect from those. derived from the vegetable Kingdom." He suggests. an unlimited supply of fat. starch sugar. because experiments demonstrate. these have not the least effect. on the production of Uric Acid. and because their large Consumption operates to restrict. the intake of nitrogenous food and therefore the formation of Uric Acid.

In patients with a hereditary tendency to Uric Acid. diathesis. as long as the Kidneys retain their normal functions and are capable of excreting all the Uric Acid formed or taken in. there does

not seem to be much Cause for interfering with their diet. Suppose the urine of such a patient fed on the usual mixed diet of ordinary life, shows no abnormality in the excretion of Uric Acid for 3 or 4 days on that diet, there does not seem to be any reasonable Cause for interfering with his diet. At the same time all excessive Consumption of flesh food should be forbidden. when we remember the experiments of Jakobaczewski, and even of vegetarian diet of a highly nitrogenous nature. when we remember the experiments of Bleibtreu and Schultze who showed (Lewin op cit p 29) that the excretion of Uric Acid during 24 hours is almost as large on a purely vegetarian diet as on a mixed diet, or even as on one in which flesh food predominates. "Even (Lewin p 85) in the pronounced form of Gout there appears no reason to forbid certain articles of food. A rational mixed diet in which the usual nutritive elements are uniformly distributed is much more to be recommended." All large meals and banquets should be avoided for indulgence in very large quantities of food are as severe a trial to the Kidneys as to the stomach and Liver, and besides at such functions there is always a temptation to Consume larger quantities of alcoholic drinks

(c) Alcohol.

than usual. In the proportions usually partaken of at meals. Alcohol seemed to exercise no effect on Uratic precipitation. in the experiments of Roberts. Still when one remembers the experiments of Chittenden. and the experiments of Levison. upon himself. (op cit p 110). and Eichorst's mention of a medical man he knew who could always produce a copious Uratic deposit. in his urine by taking a small quantity of alcohol. it seems advisable to restrict its use. both because it causes increased production of Uric Acid and its continued use diminishes the excretory powers of the Kidney in the long run

j) Medicinal Treatment.

The medicinal agents that have been employed in the treatment of Gout. with a view to Control. uratic precipitation in the tissues are alkalies such as the salts of Soda and Potash. Lithia. Piperazine Lycedine.

(a) Alkalies. These have been used both as drugs and in mineral springs. because there has been a vague kind of belief among medical men that Gout is due to an undue prevalence of acid. in the system. and that the blood was less alkaline than it should be. In some quarters it is even believed. that this is the primary vice of the gouty state. and that there exists a so-called acid-dyscrasia which dominates the whole condition.

Now. all writers who have studied the reaction of the blood. have found. that its reaction is capable of very little variation. by the administration either of acids or of alkalies. Such researches have been undertaken by Rumpf. Piper. Freudberg. (Lawson op cit p 86). Sir A Garrod made numerous examinations of the blood of Gouty subjects. and found the serum was invariably alkaline. never acid or even neutral. It Contains high powers of self adjustment. to maintain its alkalinity. Diminished alkalescence is only found in Pyrexia. Diabetes. Carcinoma. &c which have no relation to Uric Acid or Gout.

The salts of Soda. have been most frequently used to check this supposititious acidity. But the evidence we have led forward. shows how vain that proceeding is. Roberts has shown that an excess of Soda Salts. always hastens the precipitation of Bi Urate in the blood. serum. "It has been shown that the addition of an alkaline carbonate to blood-Serum impregnated. with Uric Acid. produces no appreciable effect. on the powers of maturation. and the advent of precipitation of the crystalline Bi Urate in the medium. Hence all medication of an acute attack of Gout. by Soda Salts must be set aside.

Clinical experience corroborates this. for few.

physicians have placed it on record that the Bicarbonate of Soda & the Bicarbonate or Citrate of Potash have ever produced much benefit in cases of acute gout even though given in such doses as to maintain the urine persistently alkaline. Much the same may be affirmed of Lithia Piperazine Lysidine - No doubt the uratis of these bodies are very soluble in vitro but the flourish of trumpets with which their advent was hailed has died away into disappointment under the test of clinical experience. Roberts says (op cit p 130). "If these bodies have any beneficial action in gout it is certainly not due as has been supposed to their solvent action on the material of gouty concretions."

And here it may not be amiss to point out how misleading experiments in vitro may be, compared with the behaviour of the same bodies in the human organism where one of the factors of the experiment is life and living tissue

Potassium salts seem from Roberts experiments to act more favourably than the corresponding Sodium salts in retarding Uratic precipitation. Rouchard recommends their use (Maladies par ralentissement de la Nutrition 1882). and Haig speaks favourably of their use.

Mineral Springs especially those whose waters contain a

Considerable quantity of Soda salts have ever been highly recommended in Gout. but of the previously detailed researches. are to be relied on as a guide, their value in such cases is extremely doubtful. Often one of the first experiences a patient has at such a spring is a regular attack of Gout (quite in accordance with Roberts researches). after which he feels much better. Doubtless the additional amount of Soda he has begun to take in his water has brought matters to a crisis and the soluble bi-urates floating about in his blood and tissues have been precipitated into the structures surrounding his joints. The urates are thus as effectually removed. from the vital fluids. as if they were removed by the Kidneys, and the patient experiences a sense of well-being and health. If such springs do good at all. it must be indirectly, by acting on the Liver and intestinal tract. Other springs such as those containing sulphur Sulphate of Lime, and only traces of Soda may benefit a gouty patient. but perhaps the change of scene. diet occupation, and the flushing out of the whole urinary tract with the large quantity of water taken every day. have more to do with the benefit than the chemical Constituents of the water. Infact water-drinking at home other things being equal. would do as much good. but as Roberts remarks. the other things never are equal.

The change of Scene. food. abundant out-door exercise Cessation from business worries or from the ennui of an aimless existence are some of the other things which make the difference

According to the experiments of Haig Salicylic acid given as Salicylate of Soda unites with the Uric Acid. to form Salicylic Acid which is very soluble and therefore easily excreted. There are many other points about the treatment of Gout which are of purpose - not touched on here - as only those are considered upon which the present enquiry has a direct bearing

Uric Acid Gravel

Another way in which Uric Acid manifests itself is as free Uric Acid deposited in the Urine, either in microscopic crystals. fine and or Coarser Concretions in which the crystals are connected together by an albuminous substance. As Roberts says. " in Gravel the error occurs on that side of the Kidney, and the Uric acid appears in the urine. and in the free state, and deposition takes place in what is strictly speaking. the interior of the economy, that is to say. on the surface of a doubling of the internal integument.

Naturally the question arises. How is it that

in the case of Gout. the Uric Acid is deposited in the tissues while in Gravel. the deposition is in the Urine?
What are the factors which cause in the one case Gout in the other. Gravel. .

Place of Deposit. One most evident difference consists in this that- in Gout. the deposit takes place in the blood. a living organ endowed with high powers of self adjustment. and where life is one of the factors to be reckoned with while the urine is a dead excretion. where life no longer exercises sway. but where Chemistry alone rules. and where therefore our methods of research. pursue with more hopefulness the results of its working.

Heredity. Again we notice that in both conditions. not only is there a hereditary tendency. to the manifestations of the diathesis. but that the Conditions alternate. It has often been observed. that one generation which suffers from. Gout may be followed by one. which suffers from Gravel. There seems to be a kind of vicarious Correspondence between the two. Conditions. by which the one complaint is seen to alternate with the other. at different periods in the lifetime of the same individual. But we have sought in vain. for the history of a case in which. the two Complaints were present in the same individual. at the same time. We could not help being much struck with a case to which we were called a few weeks ago

of a child suffering from Lithuria. The patient a small restless intelligent child of 6. Corresponded almost in very detail to Sutherland's description of such children. (B M Journal 1872 ½ 856) Such children are usually "precocious with small restless bodies. very changeable and nervous. sometimes extremely lively. Sometimes very depressed. They fall asleep with difficulty. sleep is short and restless and they often talk in it. They eat little and show pronounced dislike for certain foods. they catch cold readily. giving rise to attacks of pain." &c Such was the child We saw and to give point to the picture his father. a strong well-built man of 45 stood beside him with his hand swathed in bandages. suffering from a sharp attack of Chiragra. In all probability the child will grow to be one of those who "had a tendency to gravel in their youth. lost that tendency and became gouty in middle and old age."

Quantity of Uric Acid formed declines from infancy onwards.

The quantity of Uric Acid formed gradually declines from infancy to old age. In a child of 3 or 4 years of age the amount formed is .27 to .3 grms per kl. while in an adult the amount is .09 to .11 gr per lb. per day. As the formation is greatest per lb of individual in infancy on account of the more active metabolism

at that period of life. there is a greater tendency to precipitation. ~~precipitation~~ in the kidney at an early age. so much so that men such authorities as Virchow. have come to look upon such Concretions as physiological. Lewson (1874) Quotes Lahmonsen's figures. "Of 306 newly born. or very young children. Examined post. mortem. Uric Acid deposits were found in 110 Cases. and none in 166. and Lebrein gives a similar account. of 409 Autopsies in 157 of which or 38.38% these deposits were found."

Well authenticated Cases are also ~~found~~ mentioned of Uric Acid infarctions being found in foetus which died before or during birth. Such Cases go far to prove that Uric Acid is not the result of plus or minus oxidation processes. or at any rate that respiration is not necessary for its formation. In fact there is a large abundance of evidence which want of space does not permit us to Quote. all tending to show that in the early years of life. Uratic Concretions are extremely Common. and that operations for stone are far more frequently performed upon children than adults. and it is probable that a much larger proportion of children suffer from the milder form of the disease in which such Concretions are small enough to pass along the urinary passages. and be voided with the urine. This

opinion appears to be shared by. Henoch. Sutherland and da Costa. That the blood and urine should contain a large proportion. of Uric Acid in infancy. and early life. is easily understood. when we remember how active the metabolism is. in early life. and how quickly tissues are built up. and cells broken down and leucocytes shunned in the blood. while growth is so active.

But gravel and stone are by no means confined to infancy. Adults too suffer. and in some the periodical. or occasional passing. of crystals so small as to escape observation. but which give evidence of their presence. by a burning sensation in the urethra. during micturition is a sign of their diathesis which remains such thro out their life

Different tendency. of the urine to the Spontaneous liberation and precipitation of its Uric Acid

We have already seen that there are 3 orders of Uric Acid salts. (1). The Neutral Urates which cannot exist in the human body. (2) The Urates which exist and are known only. as pathological Concretions or Deposit. or in the neighbourhood of gouty joints. and (3) The Quadriurates which come into existence. whenever Uric Acid is brought into Contact with any of the body fluids. blood-serum lymph synovia. Indeed.

this order of salts. seems to be the only physiological form in which Uric Acid can exist in the healthy body. It is when it departs in one direction or another. from this normal state of combination. that Uric Acid causes trouble.

The Uric Acid found in the Urine comes from the blood. in which it is held in solution as a Quadrinate and passes through the Renal epithelium as Quadrinate. ie combined with the alkaline bases. of Sodium. Potassium and Ammonium. In a state of health. these combinations are not disturbed and the Uric Acid is thus slowly. and uniformly excreted. But under Catarrhal Conditions these normal Combinations are interfered with. and the Uric Acid is set free in the Kidneys. Ureters or Bladder. and when set free. as microscopic crystals or larger Concretions. the pathological Conditions of gravel are set up.

It becomes our task now to enquire what are the conditions under which the Uric Acid is set free.

If an acid urine is allowed to stand under Conditions which prevent. septic change. taking place. (by adding a few drops of Chloroform) Sooner or later all the Uric Acid in solution. is deposited. When Complete precipitation has taken place. not a trace can be discovered in the supernatant liquour. with Hydrochloric Acid. The time taken may vary from a few hours to a

few days. Variations of Temperature have no effect on the final result We may therefore state generally that " all acid urines have an inherent tendency to precipitate their Uric Acid. Should the precipitation take place in the Kidneys or Bladder the condition is pathological. Therefore pathological gravel may be regarded as an exaggeration of natural or normal Conditions.

What are those conditions?

Chemical explanation of the spontaneous precipitation of Uric Acid in Urine.

Uric Acid occurs in all urines even in the clear and non-sedimentary. as Quadriurate.. for Concentrate any of these even the clearest.. filter hot and Cool upon ice. and immediately a copious precipitate is thrown down which has all the physical and chemical properties of Quadriurate. ie it is amorphous and decomposed by water with a free emission of Uric Acid crystals. It might be objected that this is not Quadriurate but Bi-Urate. but we have shown Bi Urate Cannot exist as such in Urine It is instantly changed into Quadriurate.

" Therefore we may Conclude (Roberts Uric Acid p 41) without any misgiving that the Quadriurate is the form and the only form in which Uric Acid exists in normal urine.. and may draw the inference that

when Uric Acid makes its appearance there in any other guise. That event is due to secondary changes in the Quadriurate. Now regarding the Urine—

It is simply a fluid which holds in solution Urea and various extractives. and a number of mineral salts. Chief among which are. the alkaline phosphates. for they regulate mainly the reaction of the urine. Uric acid must not be regarded as merely representing a stage in the production of Urea. but as representing a special nitrogenous metabolism. It is as has been shown the result of the oxidation of nuclein. an albuminous substance which is contained. in the cell nuclei. and distinguished by its richness in phosphorus. The phosphorus set-free at once unites with the ever-present alkalis. of the blood. forming. mono- or di- metallic phosphates. and the alkalinity of the blood and hence of the urine. depends upon the abundance or otherwise. of the mono-metallic phosphates. When the mono-metallic or superphosphates preponderate the urine is acid when the di-metallic, the urine is alkaline

We have therefore in the urine exactly the conditions under which Uric acid is easily liberated. Just the Quadriurate is split up by the water. into free Uric Acid and Biurate and thus half of the Uric acid is set free. But the Biurate set free is in the presence

of the superphosphate. immediately by double decomposition retransformed into Quadriurate thus

" Two atoms of Bi Urate. with one atom of superphosphate. change into one atom of Quadriurate and one atom of dimetallic phosphate. thus. (Roberts p 42).

Bi Urate · Mono-metallic phosphate Quadriurate Di-metallic phosphate.

$$2\,MH\overline{U}. + MH_2PO_4. = (H_2\overline{U}..M\overline{HU}) + (M_2HPO_4)$$

These alternating reactions breaking up of Quadriurate. by water · into Bi Urate and free Uric Acid and recomposition of Quadriurate. by double decomposition of Bi Urate. with monometallic phosphate go on progressively till all the Uric Acid is set free.

The 1st Step is confirmed by experiments already made by acting on Quadriurate with water.

The 2nd Step the transformation of Bi Urate. in presence of superphosphate. into Quadriurate is verified by the following experiments.

A saturated solution of sodium Bi Urate.

in hot water is allowed to cool. then drop by drop. a strong solution of an alkaline superphosphate. is added. whereupon a dense white precipitate is thrown down which upon examination is found to possess.

The characteristic reactions of the Quadriurates

A similar reaction is obtained if instead

of a solution of superphosphates. the experiment is performed with an acid urine, "That the result in the latter case is not due to the precipitation of Quadriurate pre-existing in the urine is proved by repeating the experiment with the same urine after it has been deprived of its Uric Acid by repeated filtration through a Uric Acid filter"

The above change of Bi Urate into Quadriurate in presence of superphosphate explains why Bi Urates never appear as a deposit in normal and undecomposed urine. also why in the spontaneous precipitation of Uric Acid in urine. the process goes on not merely till a society but until the whole of the Uric Acid is set free.

The ingredients which retard the decomposition of the Quadriurate in normal urine.

But it will naturally be objected that if the normal form in which Uric Acid can exist in the urine is that of Quadriurate and if there is an inherent tendency on the part of the urine to precipitate its uric Acid. why does not this occur at once whenever it is voided. or even earlier. in the urinary passages. in which case every one would be subject to gravel.

There must be some inhibitory factors and if so

What are they?

It was found that this inhibitory power existed partly at least in the crystalloids of the urine.

the chief of which are Urea. the chlorides. phosphates sulphates. of Sodium Potassium Ammonium Calcium Magnesium. When the urine was subjected to dialysis and these bodies removed. it was found to have lost its power for retarding the decomposition of the Quadriurates.

The method of subjecting this question. to the test of experiment was as follows.

A speck of purified amorphous deposit was placed on a slide and carefully. mixed with a drop of the solution to be tested. The reaction was watched under the microscope. and the time taken for the appearance. of crystals of Uric Acid. was taken as a measure. of its inhibitory power. - the time of distilled water being unity. = 5 minutes.

The results were. - Urea. = no inhibitory power. Chlorides and Sulphates some inhibitory power. Potassium salts more inhibitory power. than Sodium or Ammonium. salts. Di-sodic phosphate about the same as Sodium Chloride. - None so powerful as natural healthy urine. Di-potassic phosphate gave the best results. Alkaline Urines had no disintegrating effect. on the amorphous urate.

The colouring matters.

When attention was turned to the colouring

matters. It was observed that amorphous urates were always deeply stained by urinary pigment., that deeply tinted urates were broken up by water more slowly than pale urates. That the Quadrinurate of the urinary secretion of Birds and Reptiles had no colouring matter and were more rapidly broken up by water than the ordinary amorphous sediment and that urine from which the pigment had been removed by filtering through animal charcoal acted more rapidly upon amorphous urate deposit than it did before the pigment was removed. That the deeply coloured urines of febrile states (which are also very acid) though ready to deposit amorphous urates were not at all ready to deposit free uric Acid.

Chemical Etiology of Uric Acid Gravel

(1) Retarding influences. We have just shown that the presence of salts and pigments exercise an inhibitory effect on the precipitation of Uric Acid from urine

(2) Hastening influences. Robert obtained the following results.

(a) Precipitation was hastened when the urine was poor in salts

(b). When it was deficient in pigment. and where the above two conditions do not obtain the chief determining factors of precipitation are

(c) A high proportion of Uric Acid to urinary water.

(d. The degree of acidity. The higher the degree of acidity. the quicker does the deposit take place Conversely.

The above was determined experimentally When an alkaline Carbonate was added to urine. precipitation was delayed. even when the amount of alkaline Carbonate. was so small that no change in the reaction was detectable by litmus paper. The postponement of deposition was Considerable Quite enough to have made the difference in the occurrence or not of Gravel. had the place of experiment been the urinary passages.

The results of Roberts experiments may thus be summed up. The Conditions of urine which tend to accelerate the precipitation of Uric Acid are

(1) High Acidity
(2) Poverty in Salines.
(3) Low pigmentation
(4) High percentage of Uric Acid.

} and Commonly.

Other Causes of its formation.

(1) Diet. To meet the old theory that Uric Acid resulted from the defective metabolism of the proteid elements of the food. it was considered necessary to restrict the Consumption of food of a highly nitrogenous Nature. It was thought, too highly nitrogenous food Coupled with a sedentary life and an abundant

use of alcohol. Here the factors which caused diminished oxidation of the results of retrograde metabolism and that if oxidation of these products had gone further Uric Acid would not have been formed. This theory becomes intimable not only from a consideration of Horbaczewskis experiments but also because all the most recent experiments show that Uric Acid is not increased to any appreciable extent by taking a large quantity of nitrogenous food

We have already mentioned Roberts Conclusion that Uric Acid concretions resulted from a diet poor in the saline constituents - We have an interesting object lesson in the relationship of Uric Acid of the Parsees and Hindoos who live side by side in India. The Parsees are meat eaters and in spite of the protecting influence of the climate (in favouring perspiration) suffer from Gout. The Hindoo is chiefly rice fed does not eat meat and on account of the iniquitous salt-tax consumes very little salt. His urine is therefore deficient in salines and he suffers to a high degree from stone. The same thing may be seen among poor badly fed children and among English agricultural labourers who live largely on vegetable and non-nitrogenous diet and who are very subject to stone
In Contradistinction to the wealthy dwellers in cities,
among whom stone is rare

Rice contains only .39% of saline constituents Wheat-flour .51%. Oatmeal 2.5% Milk 5.5% meat and fish 5 to 5.5%.

On the other hand. among sailors as a class stone is very rare. as their diet consists largely of salted meat. Hutchinson quoted by Le Gendre. corroborates this for he was able to find only one case of stone of the kidney among 34.000 English sailors. while this affection is by no-means uncommon among their officers. whose manner of living corresponded more to that of men on shore. ie less salt-provisions

Roberts therefore recommends. a liberal consumption of salt in the dietary of patients troubled with Uric Acid deposits or stone.

Mr Cavenagh- of Kings Lynn. (On the cause and distribution of Calculous disease. 1886. p.114). remarks that living as he does in Norfolk. the chief stone district in England. he has been struck by the Comparatively small number. of Cases of Gout. which have come under his notice. as compared with stone Cases. He says there is one part of Norfolk. the Marsh- lands. where the drinking water Contains so much Common salt. that it must be called brackish. is almost exempt from stone.

Form of the deposit.

It may exist in many forms. from fine dust which Can only be appreciated. by the microscope - to Coarse

reddish-brown grains of sand. or. to Concretions of the above agglutinated together. round some nucleus. by an albuminous Cementing substance. A good view of this Cement may be got. by dissolving away the Uric Acid by a solution of borax. and this leaves the Cementing substance exposed. as a frame-work. It is structureless. of uniform Consistence yields no evidence of cellular outline or nuclei. nor any trace of organisation According to Ebstein the Uric Acid is deposited in the Epithelium of the tubules of the Kidneys and each epithelial cell must break up. before the Uric Acid becomes free. The larger Concretions are found in the pelvis and calices. of the Kidney. smaller ones in the collecting tubes of the pyramids. and the fine sand is found in the Cortical. substance and may even be seen through the Capsule of Glisson. A Pork butcher informs me that it is no uncommon occurrence. to find Considerable quantities of coarse reddish-brown sand. when cutting open the Kidneys of pigs. Doubtless this is uric acid Sand. Sometimes these Concretions in the pelvis become so large. that they Cant pass down the Ureters. but by blocking them in whole or in part. give rise to Hydronephrosis and. other Pathological Conditions.

Pathogenesis of Gravel

It is not easy to obtain a very clear

Conception of how stone originates in the urine. especially in the upper tracts of the urinary passages. . nor why the deposition of Uric Acid in the urinary passages. gives rise in some cases. to true Concretions. which are voided while in others. it may remain there for a considerable time . without Causing any trouble. . One explanation. of this difficulty. Consists in the fact that. Cases illustrating the formation of Concretions. in their earliest stages are not easily obtained for post-mortem examination.

The evidence led forward by Roberts. shows that there are a number of factors acting separately or together which brought about the deposition of free Uric Acid in the Urine. such as. (1) high per-centage of Uric acid in proportion to the. quantity of Urine. (2) the reaction of the urine. (3) its richness in salines. especially the Chloride and phosphate of soda. and (4) the quantity of pigment. Lawson on the other hand examines how far. the following agencies. act as factors in Causing the Uratic deposition.

Heredity. Seeing as we do not know. upon what peculiarity of metabolism the Uric Acid diathesis depends. we have no means of knowing. that the predisposition operates through one of the peculiarities in the Composition of the urine to which Roberts has referred. We are able to learn very little from this predisposing Cause.

2 Age. The uric the younger it is contains a greater proportion of Uric Acid. According to Pfeiffer Uric acid appears to be produced for all ages in a gradually decreasing proportion. so that it reaches the minimum in old age in other words keeps pace with the active metabolism of the body. Concretions + Lithuria are commonest in the young.

3 Leucocythaemia. In this disease in which the production of Uric Acid rises to from 5 to 8 times the normal quantity. the formation of Concretions is very Common.

4. Other diseases. when associated with excessive Uric Acid production are liable to cause deposits eg in Pneumonia. which Von Jaksch always found to cause excessive Uricacidaemia. Deposits are Common. He says (op cit pg 6). Gegenüber den sonst so differenten Befunden bei der Analyse des Blutes bei Lungenerkrankungen, - - - - weiter den früher wiederholt etc. muss es auffallen dass ich constant in allen Fällen von Crouposer Pneumonie. welche während des fibrilen Stadiums untersucht wurden., ganz in Uebereinstimmung mit Salomon's Angaben sehr beträchtliche Mengen von Harnsäure gefunden habe". = In opposition to the usually so different results of the analysis of the blood in diseases of the Lungs. in opposition further to the repeatedly quoted observations that all the till now mentioned fevers. run their Course without Uricacidaemia it must strike one. that I constantly have found a very Considerable quantity of Uric Acid

(I have missed out a line here but I give translation).

in all cases of Crupous Pneumonia which were investigated during the febrile stage. quite in agreement with Eulomon's statements"

5. Gout. As we have already shown Gout is intimately associated. with Uric acid deposition and that it is not easy to say which is the primary affection. but as Gravel is chiefly a disease of the very young. and as such patients often develop Gout. in later life. there is something more than a presumption. that Gravel is the primary condition.

Lewins experiments on himself (with a pronounced. and hereditary predisposition. to Uric Acid Gravel). show that the proportion of Uric Acid in the urine. is not the only factor. inducing deposition of Gravel. for it may occur. both with a normal or an abnormally low excretion of Uric Acid (Lewin op cit pp 110-111.). An increased deposition was caused by. very active physical exercise. , and also when alcohol in the form of wine was taken Again we may recal the case of Richards's medical friend who could induce uratic precipitation in his urine. by taking a very small quantity of wine

6 Reaction This is one of Roberts Canons. Neutral and Alkaline urine. can hold in solution a very Considerable quantity of Uric Acid. while from an Acid urine

it is very readily deposited.

The uric Acid has no effect upon the acidity of the urine. because it always exists in solution combined with alkalies. The acidity of the urine is due to the phosphoric Acid. which unites with the alkalies found in the urine. to form mono-basic salts. and. never is found in the free state. But the acidity is brought about indirectly by the Uric Acid. for it is formed from the breaking up of the nuclein. which contains phosphorous. which is thus rel. free in the blood.. unites with bases and is excreted ~~in~~ the urine. While passing through the blood. by taking up bases it will tend to render the blood less alkaline.

Pfeiffer discovered that. the blood is less. alkaline in children (Weyl's organische Chemie. p548) i.e. at a time when more Uric Acid is formed.—

The alkalinity of the blood is also diminished by. very active muscular exercise. (Dr Hutchison Lancet. 25 Apl 1896) and (Cohnstein Virchows Archiv Bd 130 p 332. 1892). by Convulsions from strychnine.. by. Leucocythaemia. Cancerous Cachexia. Pathological Conditions of the Liver and by Fever. all of which Conditions are characterised by an active disintegration of white cells. and the liberation of the elements which go to form Uric Acid.

and Phosphoric Acid from the nuclein.

The alkalinity of the blood rises during digestion. probably because more acid is drawn from the blood by the stomach to supply the elements of the gastric juice. This fact was also demonstrated by Roberts who showed that after a meal, the alkalinity of the blood always increased, while during fasting the alkalinity was lessened. He thus divides the day into 2 parts with relation to alkalinity. One during the day when food is being taken, he calls the alkaline tide during which Uric Acid in the blood is held in solution - and the other during the night when no food is taken - during which the alkalinity lessens and attains its maximum about 7 or 8 in the morning. The morning urine is therefore particularly liable to deposit crystals of Uric Acid even when it does not contain a high percentage of that body.

A calculus found in the pelvis of the kidney has every appearance of having grown there. They have even been found branched. the branches corresponding to the calices and even extending up some distance into the collecting tubes. Ebstein affirms that these take their origin in the kidney tissue and that he has found them

in the epithelium of convoluted tubules. Probably the smaller Concretions are formed there. and in the loops of Henle and are washed thence by the flow of urine. and becoming lodged in the Pelvis are gradually added to by other Concretions. and the cementing substance is formed by the necrosed cells. in which the Uric Acid Crystals are first deposited.

Probably the latter part of this theory is incorrect for no one has seen the Uric Acid Crystals inside the epithelia. but himself. Many other authorities have observed the crystals. in the lumen of the tubes within the row of epithelial cells. as if they had been formed there.

Roberts opposes Ebstein and maintains that in Gravel as in Gout. Uric Acid injures only as a mechanical irritant. This gives a more reasonable explanation of the origin. of the albuminous Cementing substance. The epithelium is irritated by the presence. of the Uric Acid. reacts by morbid changes. proliferation and the formation of casts. This albuminous basis becomes infiltrated with Crystals. The small Concretions at first formed are washed into the collecting tubes. and the process. of irritation. proliferation and necrosis. is repeated and the Concretions increase in size by aggregation

When they reach the Pelvis, the process of aggregation is repeated, and the nucleus of a true Kidney stone is deposited. which grows by repeated additions of Uric Acid. While the Mucous Membrane of the Pelvis supplies the albuminous substance required for Cement. and thus Concentric layers are formed. in which the crystals are deposited.

Sir J Granger Stewart (Albuminuria pp 87-160). admits that renal irritation and consequent Albuminuria maybe caused by the passage of Uric Acid and oxalates through the delicate tubulles of the Kidney.

Martin-Pauge (Zeitschrift für Schutz Kunde 1875) Lewin 116). found on examining the urine of 24 Newly born children hyaline casts in 14 Cases. and on the first day of life Albumen in all. and attributed this to irritation of the kidneys. by Uric Acid precipitation.

Ultzmann. who found Uric Acid in the urine of patients suffering from temporary or physiological Albuminuria thinks that the Uric Acid is the cause of the Albuminuria, and that the deposition of Uric Acid Crystals in an acid urine. in combination. with temporary Albuminuria. a first step to the formation of Uric Acid Concretions. Abundance of evidence of a similar nature. did space permit might be given. but we shall only quote. from Lewin Myggee. observations

(Nordiskt Med. Archiv. 1878 p 23) "In 27 out of 50 Cases mentioned Uric Acid gravel was accompanied by Albuminuria. In 22 there was a trace of albumen, the sediment was examined microscopically in 25 Cases. 14 of which contained Casts. and Kidney epithelium and 3 Casts only.

In other 32 hospital cases. of Continued Uric Acid gravel. 9. suffered from Kidney disease. 10 from rheumatic affections. 10 from Pulmonary tuberculosis 1 from Pneumonia. 1 from Typhoid fever. 1 from Emphysema. In 20 of these cases the gravel was associated with albumen, but only in small amount. and temporary in character. The sediment was microscopically examined in 25 Cases. and in every one without exception. Kidney structures were found. In 24. Casts. and epithelial cells. and in 1 epithelia only. In certain cases it was established that the number of casts. was in proportion to the quantity of Gravel. Eight of the patients here referred to died. and were examined post mortem. and in Seven of these there were undoubted signs of advanced Kidney disease.

Lecorn was struck with the frequency with which Uric Acid Crystals were accompanied by Casts in the Urine Sometimes granular sometimes hyaline.

He then gives 8 Consecutive Cases from his

own practice in which this association occurs.

In Case 4. there were cylindrical aggregations of Uric Acid Crystals. like small sticks of Sugar-Candy held together by some cementing substance. having the shape and size of the larger. Collecting tubules of the Kidney. In Case 5. the urine contained threads which. on microscopic examination. proved to be branching Casts. inside of which was a fine granular deposit. probably of Uric Acid.

After so many times meeting Casts. and Uric Acid Crystals. in the urine. Lenisoni tried to prove that the explanation. was. that the casts may really originate by the deposition of Crystals. in the urinary tubules. Premising that he had a strong hereditary tendency. to Uric Acid gravel only controlled by continuous use of alkalies. he experimented on himself. He found that by Ceasing to take alkalis. both Uric Acid Crystals and Casts appeared. in his urine. and they disappeared. on resuming the use of alkalies.

Oslaser (Deutsch Med Wochenschrift 189). observed on examining the urine of patients. passing Uric Acid Crystals with leucocytes. that the number of leucocytes could be very much raised. above the average. if the patient was allowed a large

quantity of beer. He thought the casts were caused by the direct action of the alcohol on the kidney tissue but probably the cause was indirect, the alcohol causing first an increased production of Uric Acid which in the tubules caused the formation of casts

When we consider the above facts and cases, we can hardly avoid the conclusion that the deposit of Uric Acid in the tubules can set up desquamation of epithelium and the formation of casts. and that further deposition of crystals may take place in these casts. and that thus the foundation may be laid of a true Kidney Concretion.

Leuson (op cit. p124) thus sums up his Conclusions.

"When the chemical composition of the urine is such that Uric Acid becomes deposited in the kidney, the crystals are first of all laid down in the tubules of the Cortex. tubuli contorti &c. so long as they are not numerous they may be washed out by the flow of urine without giving rise to any particular inconvenience. Under special conditions, as for instance when the proportion of Uric Acid in the urine becomes suddenly increased, a large number of crystals are at one time deposited in the kidney tubules and act like a foreign body. There is then set up an irritation of the epithelia characterised by the formation of casts

of various kinds. which are in turn infiltrated with crystals. and lay the foundation of a concretion. which may reach a certain size. even in the collecting tubes. If such a minute calculus lies in the calices or in a hollow of the pelvis. it increases in size and causes. a diseased condition of the Mucous Membrane.

By means of this an albuminous substance is excreted. and deposited in consecutive layers. as the concretion grows in size. from the additional deposits of Uric Acid. This is not difficult to conceive if when one remembers the method of action of a Uric Acid filter. If Uric Acid is deposited in an already diseased kidney. and casts have already formed in the tubes. the concretions will form more rapidly: this will also be the case when pieces of necrosed tissue. or foreign bodies exist in the kidney; as they lend themselves. to the infiltration of Uric Acid crystals

If this pathological process continue for sometime. it will not only tend to the formation of larger concretions. but may also cause Chronic disease of the kidney., by extension from the epithelia to the kidney tubes. themselves and later on. may also attack the interstitial tissue. For this reason granular atrophic kidneys are very

frequently found. at the autopsy of patients who have suffered from stone of the Kidney. for many years.

This chronic. Kidney affection may early interfere with the excretory power. of the Kidney and as Charcot-States, the Uric Acid appears to be partly retained in that stage of the Kidney affection. in which the urea. and other easily soluble Constituents of the urine Can pass off. Here perhaps. lies the explanation of the fact. that symptoms of Gravel or stone of the Kidney. very often occur in younger men. who in later life are affected with typical Gout.

Symptoms.

The more crude and obtrusive indications of Renal Colic such as attendant Symptoms of nausea Vomiting and radiating pains. are well-known and everywhere described. but there are more obscure And not always. well described symptoms of the existence of Uric Acid crystals. or small Concretions in the Kidney. which. unless the physician, warned. by the existence of the diathesis. look and for. may easily be passed over. or attributed to a wrong Cause.

1. In Children Pain & Rigor. There occur paroxysms of pain in the Kidney region accompanied by shivering or feverishness.

and very often accompanied by constipation which unless the practitioner observes also that at the same time the urine is loaded with urates may easily be attributed to intestinal Conditions or to worms. and of course lead to measures for opening the bowels instead of a course of alkalies.

Haematuria. Sometimes Cases of haematuria arise which do not yield to haemostatic treatment, but when along with the haematuria its probable cause. Uric acid crystals in the urine are observed and treated by alkalies the haematuria ceases. In the same way paroxysmal albuminuria may find its explanation and treatment Similar symptoms are explained and treated by Sutherland (in B M J annual 1872 p 856).

Pain referred to the Umbilicus. is very frequently a symptom in children and may easily be misunderstood but when it is associated with pain in the loins. or a copious deposit of Lithates. its true character may be surmised. It should be remembered however that children seldom Complain of pain in the Kidney region but generally refer it to the umbilicus.

Often there is an access of unaccountable indisposition tiredness. and depression. Changeable disposition and low-spiritedness without Conceivable

Cause. which may even advance to a state of complete melancholia. and which is often alarming because there does not seem to be. any adequate Cause for it.

In Adults. The most Common Symptoms are.

(1) A dull pain over the loins occupying the position of one or both Kidneys. It is more nearly a tenderness. rather than a pain. and is not increased by pressure. but is aggravated by the patients lumbar region occupying a position of Constraint for some time

(2) Pain radiating in various directions. especially towards the left Hypochondrium. or between the shoulder-blades. may be mistaken for some gastric condition. If it radiate to the thighs it may simulate Sciatica. though it is differentiated from that Condition by adhering to the outer and anterior aspects of the thighs following the distribution of the Cutaneous Crural Nerve.

(3) Various Neuralgias

(4) Constipation

(5) Piles

(6) Periodic States of depression. without hallucinatin tendencies. with tiredness. sleeplessness and loss of flesh. almost always accompanies the repeated painful sensations characteristic of Gout. the formation.

of Gravel. These symptoms correspond with those characteristic of Heigs Migraine Similar Symptoms may be caused by deposition of crystals of Oxalate of Lime in the Kidneys.

Treatment.

There are 3 objects in view.

(1) To act upon the reaction and chemical Constitution of the urine. in such a way as to diminish the tendency to urates precipitation

(2) To decrease the amount of Uric Acid produced. when there is reason to think it is formed in increased quantity.

(3) To endeavour to eliminate or dissolve Concretions already formed. in the Kidneys

Diet. These objects are sought to be obtained partly by the regulation of life. and diet and partly by using drugs.

The diet has been varied in many ways. according to the theory at that time in favour thus Cantani recommended a diet in which flesh preponderated. Haig a diet from which flesh in all forms was carefully eliminated. and Ebstein the same diet he prescribes for obesity and Gout.

The statistics which have been collected.

seem to show. that a diet too poor in albuminous substances. has a tendency to cause Uric acid Concretions. and in this connection we ought to remember. Roberts demonstration of how. Uric Acid crystals are frequently formed. in the urine of poor badly fed children. rice-fed Hindoos and the vegetable-fed. agricultural Labourers. of England. and especially of Scotland. and the recorded. instances of uratic abundance during prolonged fasting.

Alcohol. should be avoided. both because it increases production. of Uric Acid and also. because it tends to produce retention by irritating the Kidney tissue. by the precipitated Uric Acid crystals.

Much drinking of water. as tending to make the urine. very dilute should be avoided because Quadrinvales decompose. more rapidly in pure water than in urine. At the same time as much alkali should be taken as to keep the urine neutral or faintly alkaline remembering that Uric acid is never precipitated from alkaline urine

Regulation of Meals. is important when we remember that the acidity of the urine and therefore its tendency to deposit crystals of Uric Acid. are always greatest after prolonged fasting.

Lactic Acid. A considerable quantity should be taken daily as it has been shown. experimentally (Roberts) to hold.

Uric Acid in solution." The richer it is in salines the less the tendency to precipitation".

Alkalies. exert a favourable influence on the reaction of the urine in keeping it neutral or alkaline. Though in some cases they seem to increase the excretion of Uric Acid. Dr Haig would explain this by saying. they tend to bring the Uric Acid already deposited in the tissues through the blood. by increasing the alkalinity and therefore the solubility of the blood for Uric Acid.

Where the Concretions are too large to pass down the Ureters. such means should be employed. as are capable of dissolving the Concretions. The Compounds of Lithia have been most in favour for this purpose. Chiefly because the urate of Lithia can be shown to be very soluble in water. Clinically however. and in practice. Lithia has been pronounced a failure by many Competent observers. Roberts (op cit p 130). Says. "of these bodies. (Lithia & Piperazine). have any beneficial action in Gout. it is certainly not due as has been supposed. to their solvent action on the material of Gouty Concretions". Robert Reese (Gout p 207). Says. "When however Piperazine is dissolved in urine the solution has little if any action upon Uric Acid. and experiments have likewise proved. the drug has no influence upon the formation of the latter substance". This

Lithia and Piperazine.

a strong testimony after using it in 30-40 Cases.

Indeed. Lithia has been shown to diminish the excretion of Uric acid. It has been pointed out in the Lancet for 1860 p 185. But in (Ross's Chemistry Analysis p15).

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. as with the triple phosphates of Ammonia and soda. Salts generally present in animal fluids"

Hence. Chemistry and Clinical experience agree on this point. and give us. another warning. against jumping too hastily to Conclusions from experiments. in vitro. Indeed the same warning is applicable to all experiments. in which physiological processes. are supposed to be imitated. by experiments in test tubes. The one thing wanting is "Life". The power which Changes the Conditions of the experiment materially.

Lycidine. We have heard however. witness lately the result of Dr J Woodcock Cumberbody. to the Brit. Med. Association. on the result of his experiments with Piperazine & Lycidine (BMJ annual for 1896. p 901) The conclusions he came to are.

"Piperazine & Lycidine when added to a urine tending to deposit Uric Acid gravel. are capable of hindering the deposit during standing. Lycidine is a more powerful solvent for Uric Acid than Piperazine.

Both Piperazine and Lycidine when taken internally

appear to increase the elimination of Uric Acid.,
not by increasing its formation in the organism. but
by rendering the blood more capable of removing it
from the tissues. by increasing its solvent-power. so
that prolonged administration of these drugs. in the
end causes a diminution. in the quantity of Uric
Acid. eliminated by the Kidneys.

Piperazine and Lysidine are both diuretics
and cause an increased elimination of Nitrogen
which is partly due to the increase of the nitrogen
in the uric Acid and in part due to its diuretic action"

Urea. Dr. G. Klemperer. in a lecture reported. in the
Berlin Klinische Wochenschrift 17 Aug 1896. p 732 seqs.

Des Weiteren haben wir zahlenmässig festzustellen
gesucht. wie auf die Acidität des Harns. diejenigen
Mittel einwirken welche in dem Rufe. stehen. besonders
als Lösungsmittel der Harnsäure zu dienen. Wir
untersuchten zuerst. den effect der organischen Basen
Piperazin. Lysidin Urotropin. welche in Reagenzglas.
so grosse Mengen. Harnsäure zu lösen vermögen
und welche nach den Angaben vieler Autoren auch
dem Urin ein grosses. Harnsäurelösungsvermögen verleihen

Unsere Versuche zeigten dass die Organischen
Basen. in der That unzersetzt. in den Urin übergingen
und nicht etwa unter. NH_3- Abspaltung zersetzten.

Thatsächlich wird durch diese Anordnungen die Acidität
des Urins vermindert. wie aus folgenden von Bunchi erhaltenen
Zahlen hervorgeht usw. =. Further we have sought to
determine numerically. how these means. operate. on the
acidity of the urine. which are in reputation especially
to serve as means. for the solution of the Uric Acid. We
investigated first the organic bases. Piperazine Lysidine
Urotropine. which in the test-tube are able to dissolve
so great a quantity of Uric Acid. and which according
to the statements of many authors. also lend to the
Urine a means of dissolving Uric Acid. Our investigations
showed that. the organic bases. in reality pass over.
into the urine. unchanged. and do not- change (sich zersetzten) become analyzed into
at all into Ammonia-products (or formations). - As a matter of fact-
the acidity of the urine is lessened. through These
Ammo-bases. as is seen from the following Tables &c.

We then asks. whether. man outside of these bodies
together with. the regulation of diet. abundant use of
fluids. and especially of alkaline waters. there were still
other means which in an specific manner. could dissolve
Uric Acid. and his Ammon is. (1733). Dass die.
neben den genannten. organischen Basen. noch
auch das Lithion vermögen, brauche Ich nicht nochmals.
auseinander zu setzen. Diese Mittel gehen in den
Urin über und vereinigen sich mit den vorhandenen

Mengen derselben. so dass 2/3. der grösste Theil. des eingenommenen Lithions als Chorlithium und nur ein Kleinster Rest. als. harnsaures Lithion zur erscheinen vermag. = That neither the above named organic bases. nor even Lithia are able to do this I do not require to explain once more. These bodies pass over into the urine. and unite with the existing acids. according to the pre-existent quantities of these so that, for example, the greatest part of the Lithia which has been taken appears as a Chloride of Lithia. and only a small remainder. is able to appear as Urate of Lithia. (I need not give any more of the text but simply the translation).

"There is one body. which can dissolve Uric Acid. independant of the laws of the operation of Masses. and quicidity. that is a substance whose mode of action (Wirkung). has been known for years. and which yet is only little employed. because there has never been any Commercial demand for it. Urea.

Six years ago. Rüdel established in the pharmacological institute at Heidelberg. that Urea is able to dissolve Uric Acid. He brought forward this circumstance in order. to show why in normal urine. so much more Uric Acid can be dissolved than is possible in water. Thereupon Moring recommended. that

Uratic patients should be allowed. to eat much meat. for he who eats much meat has much Urea in his urine, But I believe he who allows his patients. for this reason to eat much meat. wounds him with the one hand in order to heal him with the other. It is better. that one should avoid abundant Uric Acid formation. through eating meat. and give to his patients Urea ready made. (Fortiges Präparat)

In this way has Rosenfeldt. in Breslau. employed it once last-year. and in this way (as I have shown in the report. of the last Congress. für Innere Medicin. it has been lately employed by many Clinicians".

"I myself have proved for almost 2 years. in a great measure. the therapeutic use of pure Urea. I believe I may venture to say. that. this material offers. an excellent means. against the uric Acid diathesis.

I give it to such patients as have passed. Uric Acid concretions. and who once again more. suffer from Colic (renal) or rather Haematuria. I do not fail. once more to point to the well-known fact. that an abundant supply of pure Urine fluids. in many cases. under suitable circumstances. can deliver the patients from the symptoms without Urea. but any Doctor will willingly possess a means. which can alone perform the same (service) as the

now- established method. (die bisher exprobten Methoden)
I prescribe.

Theae purae. 10.0 (= 20

Aquae destillat 200.0.

~~Da m dtt~~ Secundis horis 3ß.

I have not seen harmful Consequences. from this Medicament. although I several times have prescribed upto 500 grms. Consecutively. A much desired consequence. is the often remarkable increase in diuresis upon which I have made remarks in another place".

The above fact was also established by Bouchard. who refers to it in many places. in his Autointoxication. On p60 he says. while recapitulating the toxic principles. which he demonstrated in Urine. " we find there are seven of them, There is first a diuretic substance. fixed. of organic nature. since it is destroyed by heat. It is not fixed by Carbon. it is soluble in Alcohol. and we find it mixed in the alcoholic extract. along with the other substances which have different properties. This substance possesses. besides. the preceding characters. the property which experiment allows us to attribute to them. that of augmenting the quantity of urine. We have thus the right.

to say. that this diuretic substance contained in normal urine. is no other than Urea. Urea in this way. although it is a product of dis-assimilation. plays a useful rôle in the economy. it possesses the property of forcing the renal barrier. of removing whilst making its own escape from the organism. both the water in which it is itself dissolved. and the other toxic matters which are united with it". This may be the way in which Urea causes also increased excretion of Uric Acid in Klemperer's experiments. The other points insisted on by Klemperer are.

(a) There must be sufficient diuresis. One gram of Uric acid requires 7 litres of water for its solution at the body temperature: the patient must therefore drink a sufficient quantity of water.

(b). Much sweating and much exercise should be avoided

The treatment of Gravel differs in this respect from Gout.

(c) The quantity of Uric Acid in the urine should be diminished. for Uric Acid must not be regarded (as has been shown Seppra) as representing a stage in the production of Urea but as representing a special nitrogenous metabolism. Care therefore should be had as to the kind of food taken. Uric acid excretion on a milk diet is scarcely any greater

than during fasting. There is no general quantitative relation between the nuclein in the food and the Uric Acid in the Urine (Horbaczewski). for nuclein may also be excreted as Urea. just as Uric Acid may be. when taken by the mouth. (opposed to Haig's teaching). The difference in different individuals seems to depend on some persons being able to transform the Uric Acid formed in their bodies more readily into Urea than others can The ingestion of Xanthin bodies leads. just as the taking of nuclein does. to an increase of Uric Acid in the urine therefore excess of Tea Coffee and meat extracts should be avoided. (Confirmed by Haig).

(2). The acidity of the Urine should be kept below a certain level. to prevent the precipitation of Uric acid. He therefore recommends. Liq. Carb. or Pot. Citrat. in the forenoon. and late in the afternoon.

It will be observed. that Rheumatism has not been regarded. as one of the manifestations of Uric Acid in this paper. Some writers of great authority regard both these conditions. as caused by Uric Acid. We are unable to come to the conclusion after much reading and study that the factor common

To these two Conditions is Uric Acid but are inclined rather to look upon the Arthritic Diathesis as the Common factor. It is too late to discuss the question here but we may be permitted to indicate the grounds of our belief.

Arthritism (defined originally by Bidouse and accepted later by Charcot and Hutchison) is a diathetic habit of body from which arise as branches two main and distinct classes of disorder. Commonly recognised as Gout and Rheumatism.

In the most recently published work on authority on Rheumatism (Rheumatism by Madigan 1896) not a word is said about Uric Acid as a Cause in Rheumatism: but Lactic Acid is shown to be the offending material ... "a product of mal-assimilation or imperfect tissue metabolism" (p 20). On p 51. he says "Increased formation of Lactic Acid is one of the essential features of Acute Rheumatism, and no theory of that disease (Gout) can be regarded as satisfactory which does not recognise and account for this increase. This the lactic acid theory fails to do." and again in p 59 et seq. "the fact which has been demonstrated by Garrod and others over and over again that Uric Acid does not exist in excess in the blood in Acute Rheumatism" When Lactic Acid is

the Cause of disease in a patient of arthritic diathesis. It is known as articular Rheumatism. But where the arthritism is not the outstanding feature. Muscular Rheumatism is the result.

Besides the pathological allies of Rheumatism are Malaria (Neuralgia) Chorea. and Erythema not Gout and Gravel.

On the other hand. Uric Acid manifests itself in Gout and Gouttiness. The one state may never pass into the other. but more commonly Gouttiness inclines towards Gout and Gout once declared passes sooner or later into Gouttiness. Their aetiology is the same. and we have no choice left but to regard that which they possess in Common. as the essential part in them. and that which is not Common. in their manifestation as the non-essential part. So also with Gout and Rheumatism., the Common factor is the Arthritic diathesis. Viewed from this point also. it is easy to Conceive why the same patient may be afflicted. at one time with Gout and at another with Rheumatism.

Highly as we value the opinions of Dr. Goodhart we cannot agree with him nor find sufficient support for his statement in his paper. (B M Journal 1891 ij 252).

that " in summing up what Gout is we must say that under some circumstances or at one period of life Gout is Acute Rheumatism."

We feel bound to say his ~~proof~~ evidence does not justify that conclusion.

We feel constrained also to admit that Uric acid is not the only factor in Gout. If it were, then Gout would be one of the characteristics of Leucocythaemia. It should also be found very frequently in children who produce Uric Acid in great quantity. and it should always result from those habits of life and diet which lead to daily and excessive proliferation of Leucocytes.

Were renal disease, in itself capable of bringing about the Uric Acid disturbance and Gout. all cases of Renal disease should develop Gout sooner or later. This is far from being the Case.

There is much too that we do not know about the urate deposit. eg. we do not know whether the urate deposits are imported into the joints or produced there. whether they occur in absolutely healthy Cartilage or only after previous damage or disease - whether the deposition is always preceded by a degenerative or ulcerative process. as maintained by Sobotta (see note). or whether it is not rather the cause of the irregularity

pitted or excavated surface of the cartilage. We have no absolute evidence that in acute Arthritis the acicular deposit is the cause of the pain and of the Inflammation. Much evidence tends in another direction. For example. the rapid disappearance of the inflammation from the great toe under the influence of Cold effusion - of colchicum. (the peculiar benefit of Colchicum is not seen in any other inflammation. See D Duckworth op cit - p 31-5). or of other means. is not easily explained by the assumption that its cause. is the mechanical irritation of the Bi-Urate.

Summary.

We have endeavoured to show in the preceding pages.

1. That Uric Acid is formed in the body by the disintegration of the albuminous substances of its tissues especially of the nuclein (Horbaczewski).
2. That its excretion becomes increased or diminished by all factors. (diseases drugs. poisons). which give rise to a more rapid or slower disintegration of tissue (Horbaczewski)
3. That in every individual. the excretion of Uric Acid remains nearly constant after the 12th hour of fasting. but that after a meal. the excretion of Uric Acid rises rapidly. and does not sink again for several hours. ; that an increased excretion of Uric

takes place later. reaching its maximum 4 hours after a meal. and then falls again. As a consequence we infer that Urea. is derived from the albumen of the food. and Uric acid from the tissues of the body. (Maress).

4. That the taking of food. especially flesh food. causes a temporary (digestive) Leucocytosis. which arises from the nuclein of the ingested food. or from the increased cellular activity during digestion.

5 That the Leucocytosis which accompanies digestion. is the cause of the increased excretion of Uric Acid after meals. (Horbaczewski)

6 The fact that Uric Acid excretion is greatest in infancy and least as age advances. in fact keeps pace with metabolic activity. favours the same theory.

7. That this Conclusion is supported by much collateral evidence. which may be summed up in the statement. that an increased Uric Acid excretion goes hand in hand with an increase in the number of Leucocytes. whether physiological as in infancy and childhood. (Martin and Ruge and Pfeiffer). and after ingestion of nuclein (Horbaczewski). or pathological as in Leucocythaemia. (Lauche. Bentels Stadthagen and others). in Pneumonia. Cancer and extensive Burns. and after the exhibition of Pilocarpin (Horbaczewski). after Alcohol (Chittenden. Cancer. and Levison). and after unusual physical

excretion (Lawson Hutchison).

8. That Uric Acid production is not dependant on destruction of Leucocytes alone. but also on the disintegrative and metabolic changes. in the totality of the organism. changes which are influenced by alimentation (Lawson). but not in the proportion of the nitrogenous ingesta. while the production of Urea. is strictly proportional to the latter.

9. That whenever elimination is interfered with. as in Kidney disease Uric Acid accumulates in the blood.

10. That the normal or physiological form in which it exists in the blood, or is excreted in the urine is that of a Quadriurate of Sodium Potassium Calcium Magnesium &c (Bence Jones. and Roberts).

11. That the pathological form in which it is found in the body. is that of a Bi-Urate in Gouty Concretions and Tophi.

12. That the Quadriurate circulating in a medium. rich in Sodium Bicarbonate gradually takes up an additional atom of base. and is thereby transformed. into Bi Urate which is less soluble. and also. (either for that reason or because it is a Compound. foreign to the normal economy.) less easy of removal by the Kidneys. The Bi Urate thus produced. exists at first in the hydrated a gelatinous form.

but with lapse of time and increasing accumulation passes into the anhydrous. or crystalline condition. and is then precipitated as Gouty Concretions or Tophi.

13. That the factor which seems to have the greatest determining influence. as to the site of deposit. is the abundance of Sodium in the tissues; thus fibrous tissue contains Sodium in greatest abundance. and therefore Biurate is found. deposited chiefly in fibrous tissue.

14. That it produces its deleterious effects. by mechanically acting as a foreign body. in the situations in which it is deposited. (Roberts). and is not toxic in any quantity in which it can be injected into the veins (Bouchard).

15 That also after excretion in the urine it may under certain conditions become the cause of much injury throughout the Urinary tract.

16. That all acid urine has an inherent tendency to precipitate the Uric Acid from its solution as Quadriurate. as fine sand or larger Concretions of Uric Acid (Roberts.

17. That the conditions. which tend to cause or hasten. this precipitation are. (a) absence or poverty of salines. and pigments (b). a high proportion of Uric Acid. (c) a high degree of acidity. (Roberts).

Other determining agencies are. (1) heredity (2) age. - the younger the urine the greater the proportion of Uric Acid. (3) Leucocythaemia (4) Other diseases as Pneumonia (Von Jaksch) Gaul. (5) Very active physical exercise (6) Alcohol. (Lewin. Eichhorst).

18. That probably the most efficient factors in causing precipitation are. - high proportion of Uric Acid to water. - and high degree of acidity.

19. That Uric Acid manifests its presence in different ways in different patients. according to their underlying diathesis - as. Gout or Gouttiness.

20. That Gout occurs. when excess of Uric Acid manifests itself in a patient of arthritic diathesis.

21 That Gouttiness occurs. when Uric Acid in excess is manifested in a Patient without this underlying diathesis. and consists in a general change. both functional and structural - the functional change as it affects the ~~tissues~~ Juices. is abnormal acidity (ie lessened alkalinity). and as it affects the Tissues increased irritability and lowered resistance It is most manifested in the Nervous system by a great increase of excitability.

22. That Uric acid is present in least quantity in the body in the highest conditions of health.

That in disease States commonly increase

and this is an indication of a lower level of metabolism constituting a degradation to a lower animal type (Sir W Gull quoted by Sir D Duckworth op cit p 37)

23. That the excreting functions of the Kidney. for Urea. and Uric Acid. are separate and independent of each other.

24. That as regards treatment. while Sodium salts are all powerful to prevent precipitation of Uric Acid in the Urine. they are of no value (as has been maintained). because solution of Urates deposits in the tissues. In opposition to this experimental testimony we feel bound to point out. that clinical testimony points to an opposite Conclusion. as far as the value of Sodium salts in Gout is concerned. for they are largely prescribed especially on the Continent and largely taken also (as mineral (natural) waters). in spite of the experimental evidence which has denied to them any important direct solvent power. for Urates deposits. and placed them under Suspicion. of increasing their precipitation.

25. That great Care should therefore be taken in adopting. the testimony of experiments in vitro. especially when they are Contradicted by Clinical experience. We

ought never to forget the difference
in the behaviour of the chemical atoms
and molecules when left to the definite
interaction of chemical affinities, compared
with the conditions under which in a
living organ as the blood. Life takes
hold of them and determines their relationships.