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Uric Acid.

Etiology

Physiology

Pathology

and Treatment, as far as is suggested by the previous enquiry.

by

Alexander Dall, M.A., M.B., F.R.C.P.
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 Protein
forms, included under the general and somewhat
indeterminate term Goutiness.

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 peculiar 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 exhaustive study of its Metabolism: Physiology,
Chemistry, and Pathology. For only upon such knowledge
can these rational and definite principles of prophylaxis
and treatment be founded.

But Uric Acid always manifests its presence
clearly and unequivocally, as the 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 urea 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 secretion are extremely narrow, its presence in the body assumes a position of greater importance.

Though it manifests itself chiefly in the form of urine and gravel, and 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 (Craonian Lectures 1892 p58). He says that many people, are never troubled with gravel and conversely. In both there is an abstraction of this Acid, but the error is essentially different. In the two cases, both as to site and to nature in one the error occurs on one side of the kidneys, in the blood and tissues, and the urea acid is precipitated in a state of combination as Riuota. In gravel the error occurs on the side of the kidneys, and the urea 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, which latter the deposit occurs in what is strictly speaking the exterior of the economy.
The surface of a doubling of the external integument.

Moreover it 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 abnormally 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, whenever it exists in abnormal quantity. Frequently when pathological conditions are present in any system a gravity or uric acid colouring is given to the disease. Hence the use speech times as Chorea, Rheumatism Suppressed, or Retrocedent Scurvy.

Vesical Chills, County Nephritis and Pericardia.
County Skisi disease, County Disease of the Throat. (See Dr. Macrae). County Asthma and Bronchitis reappear in connection with these cases being known by the fact that they disappear upon the suspension of classical and typical attacks of Pneumonia or Chorea.

In such cases it is of the utmost importance to
be able to recognize. The underlying "diasthesis" (a faculty much praised and enjoined upon his students by the late Prof. Laycock.) for all treatment will be in vain till that is recognised and allowed for.

Before proceeding to the complete study of the Etiology of Urate Acid, and the laws of its chemistry both in the blood and urine, it will be advisable 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 about command, during the last 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 standpoint of today, contain novel elements 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, one finds the two great schools of pathology. the Animal and the Vitalist. But from our point of view, these two conceptions are as inseparable as the fluids and solids of the body are. Stated crudely, the Animalist theory is this: The fluids found in the alimentary canal, in the vascular system, in the secreting and secreting glands.
and in the tissues themselves are the agents of disease.

The last of the great apostles of the "Humoral" theory was Sydenham who adhered to the view that in Catarrh the blood is vitiated through the defects or disturbance of the secretions especially the hepatic and digestive secretions.

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

Scheele 1775: 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 Cystitis. Concretions, but it was挠ed for Starnd to point out the connection between Uric Acid and Cystitis. By demonstrating the presence of Uric Acid in the blood and tissues of the Cystitis. By his well known thread experiment which today is demonstrated to and repeated by every Tyro in Medicine at all the schools.

Mechanical Theory

Hansen showed that Uric Acid caused damage not while in solution in the blood, but when deposited as Bile in and about the Tissues.

Uric Theory

Latter T. Hoag while not denying the above maintained that Uric Acid manifests its deleterious action while in solution and circulating in the blood.

 considem Tonic

Then Ostern combines these views and conceives a double and reciprocous influence tonic on the one hand and mechanical on the other, between the tissues and the Uric Acid.

But better than a historical classification is the
following one, for which I am indebted to Dr. War
on his book published (Oct 1896) after this paper
existed in rough form and which I have adopted
as superior to my own. (Nov 22).


1. Chemical Theories.

A. Carroo's Theory of Urine Acid excess and Remote Inadequacy.

Practically in all the following theories urine acid
is regarded as the peculiar materia 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 urine acid in the human body. The arbitrament
of the experimental method and to show how this has
been done practically by some workers and partly by others.

Carroo's Theory.

The phenomena of heat are dependant
on the pre-existence of urine acid in the blood and
their local manifestations are due to its deposition
as crystalline sodium biturate 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 urine 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
imperfection of the blood. (Carrod, A Treatise on Genito-Urinary Disease, pp. 274-5).
He sums up his conclusions as follows. (Carrod, 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 before and at the period of the seizure, and is essential to its
production, but this acid may occasionally exist 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 lengthy 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,

affliction subsequently becomes structural. The urinary
secretion also becomes altered in composition.
The impure state of the blood... arising principally from
the presence of urate of soda, is the probable cause of
the disturbances which precede the gouty seizure, and
many of the anomalous symptoms to which
sufferers from gout are liable.

The causes which predispose to gout independently
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.

The causes exciting a gouty fit are those which
induce a less alkaline condition of the blood,
or which greatly augment the tendency of the formation
of uric acid, or such as temporarily check the
eliminating power of the kidneys.

In no disease but true gout is there a deposit
of urate of soda in the inflamed tissues.

Pfeiffer's 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
induced by the pain and hyperacidity of a gouty attack.

It finds support for this theory in the clinical
observation that, "in quiet conditions pain is increased after the administration of alkaloids, while it is relieved by acids, especially salicylic acid in large doses."

The objection to this theory is found in the so-called "Robl's experiment", by which it showed that it is extremely difficult to make much impression on the reaction of the blood by administering acids or alkaloids as they are quickly excreted by the kidneys. Freidelberg (Virchow Archiv, B. 125, p. 566) and others have confirmed this fact experimentally.

**Ehrenreich's Theory.**

The destructive action of tubercles on the tissues. According to Ehrenreich (Beiträge zur Lehre von den hämorrhoidalen Tumoren, 1870, p. 23), pain depends upon an abnormal excretion of the sources of the supply of urine acid. It is found in abnormal situations of the urinary bladder. Cartilage muscle, tends to manufacture acid, and may be produced in these tissues, in abnormal amount. The presence of urine 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 urine contained in the stagnant lymph-stream has time to act. Necrotic changes are set up, and as a result the tissues change their alkaline reaction to an acid one. At that moment a precipitation of sodium bicarbonate takes place, and an attack of gout begins. When such a deposit is afterward dissolved off, a necrotic empyema is
incidentally exposed, and [illegible] finds in this the confirmation of his theory.

That Urë Acid is formed in various tissues not usually concerned with its formation is disputed by Horakovsky's finding that in health Urë Acid is a by-product of the metabolism of almost all tissues. (monohydric sugars)

Well when documenting the formation of non-necrotic patches in the scrotum, head, by liquefying the muscles of birds and serpents. He was not imitating a physiological process, or even a pathological one, but reproducing the conditions of thrombosis, and no condition similar to gest.

2. Modified Chemical Theories.

Theories of Hepatic Insufficiency (Munchausen + Lathurn). Functional rearrangements of the liver 22nd ed. (disease) 1874.

A. Munchausen showed that in addition to the secretion of bile and the formation of glycogen, one of the chief functions of the liver is the destruction of albuminosa.

matter derived from the food and tissues, and the formation of urea and Urë Acid, which are eliminated by the kidneys, and that deposits of Urë Acid and urates, and in imperfect formation of these, are frequent causes of functional, as well as of structural rearrangements of the liver. At the same time he admitted renal insufficiency and, as a consequence, accumulation of Urë Acid in the blood; were associated factors in the production of gest.

B. Lathurn's view: (On the formation of Urë Acid in animals and its relation to dye and enuretic 1984).
According to this view, the imperfect metabolism of glycemic is the primary and essential defect in the formation of uric acid, and that therefore, functional aberrations of the liver is considered to take a prominent share in the causation of these conditions.

In Diabetes there is an inability to effect the metabolism of glycemic which then passes into the circulation, as in Council and Chavel. The imperfect metabolism of glycemic is the "fourUDGEmale." In his Council Lecture for 1916, he says of the glycemic of uric of it "fails to be absorbed," "metabolized," it passes from the alimentary canal, or elsewhere into the liver, there under the action of the gland, it is conjugated with uric acid resulting from the metabolism of the other amino bodies, serine, etc., and is converted into uric acid, it then passes on to the kidneys, to be combined with other molecules of uric, to become Ammonium Uricate, a portion of which is thrown into the circulation, and is converted into Ammonium 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 stimuli become somewhat paralyzed, 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 glycemic.

The objective 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 expected change. There is not a single word of experimental proof.

C. H. Hering's Theory. (Uric acid in Connection with Disease, May 3rd, 1896)

Uric acid in the blood, acts directly or through the renal motor centre on the muscular fibre of the arterioles, causing increased pulse, tension, and blood pressure, and therefore migraine epilepsy.

This theory stands alone in originality and in the unhesitating boldness with which it is stated. It does not, to inquire what preceded uric acid. He accepts Hering's theory of its formation, and quite are not too fastidious about the stability of his mid-air formulation. Everything is evolved smoothly on the lines of the theory.

This book (of c.xt.) is charmingly written and stimulating to read. Because one must stop so frequently to compare his physiology and pathology with the same section of a catastrophe.

I give his theory at considerable length because it is hard to exaggerate an extent upon the experimental work. Since this theory is based largely upon numerous unmerit of his own, the work for which few men would have such courage.

From his youth he suffered from headache.

He tried drugs in vain. Then he tried change of diet - no meat, only milk and fish - then his headaches fell from one a week to one a month, then one
every 3 months. Then every 6 - 8 - 12 months.
and eventually one in 18 months. And I returned
the return is made to meat diet. Then he began
to seek for an explanation of these phenomena. and
found that migraine had every strong relation to Gaunt
and therefore began to suspect Uric Acid might
turn out to be the cause of his trouble.
He then began to estimate. his secretion of Uric
Acid and tried and found a definite relation between
the Headache and the excretion of Uric Acid.
He found that E Clowes in his work on Migraine had
described concomitant symptoms. e.g. slow high tension
fever. cold surface and extremities. mental depression
dehydration for occurrence. The urine passed during
the Headache. slowly. 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 from hour to hour.
(Transact Phys. Vol. VII). His next point
was that by altering the excretion of Uric Acid he
could alter the symptoms related to it. e.g. increased
excretion of Uric Acid produced by Taking an alkaline
always cured the concomitant symptoms. i.e.
Headache. Mental depression. Cold surface and
extremities. Blax pulse. Sowt urate. When the
alkaline excretion stopped. he symptoms stopped.
In this gained (Lost elit p. 3). Power to produce o
He observed that whenever an acid was given to diminish the secretion of Urine Acid, he always experienced walking and shooting pains in his joints (generally the most used on the day in question). He therefore concluded that the Urine Acid was held back in these joints and caused the pain, and that the Urine Acid which failed to appear in the Urine must have gone somewhere and (as it was most natural to suppose) into the joints. He found that I am not described similar pains, when many patients took beer or wine—all which he found broke the acid, and therefore seeing his theory thus confirmed he considered it established. He then says:

General Law: (See p. 5) "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 Urine Acid increase its secretion 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 Urine Acid, diminish its secretion in the urine, and also increase these irritations in joints and other fibrous structures which are due to its presence."

He showed 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 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, Anaemia, etc.

If it be granted that Uric Acid affects the arteries 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 this discovery is a fact which neither James 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 solubil alkali in the circulation. The quickest excretion of the day occurring in what Roberts have called the alkaline tide, and the smallest excretion in the high acidity period of the night.

He acknowledges his indebtedness to Sir Lees's work for a knowledge of the relationship
of Migraine to Epilepsy, and of both to Seizures — and to Dr. Bois Raymond, for a suggestion of the relation of Epilepsy to Migraine.

He states his next discovery as follows: (p. 211 p. 8).

I found 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 out into the urine. So that, if 12 grains can be obtained from the urine, 10 or 11 grains can at once be retained. (11th Plp. vol. 471).

(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, merely by taking that substance by the mouth, and thus anyone who wishes to do so can repeat my experiments and satisfy himself as to their truth.

His second discovery he states as follows: (p. 211 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, Hemoglobinemia, and other diseases and also counteracting the effects of iron and preventing it from building up the blood and curing these diseases.

Formation and secretion of Uric Acid.

He noted that on a day on which he had a severe headache, the secretion of Uric Acid was...
He grans 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 reconciled with. He observed that on
the day, with no Headache, the relation of the
excretion of Uric Acid to Urine was as 1 : 30; while on the day with the Headache the excretion
of Uric Acid to Urine was as 1 : 20. He accordingly
set about investigating what the normal relation
of Uric Acid to Urine was. As the result of laboratory
experiments over 10 years, he came to the conclusion
the relation was: Uric Acid : Urine :: 1 : 30.

He keeps his Urine about the physiological level
by eating substances which contain sufficient nitrogen
but which introduce into the body little or no
Uric Acid in what amounts to the same thing Tannin base.

As far as the Headache was due to Uric Acid
it is due to a fluctuation in excretion. No alteration
in formation has necessarily taken place. He
quotes similar figures obtained by Inglis, or
Bailey, (Annals de Med. Sept. 1888), who found as the results
of their experiments. The relation here from 1:30 to 1:40.
Dr. Crichton also quotes Lennard-Jones figures, as 1 : 35. (Journ. Anat. Jan. 1908)

When the Uric Acid formed in the body
is introduced in a day in food, is excreted there is no
Headache because no excess of Uric Acid was held
in the blood. When more is excreted than formed
the surplus comes from the parts of the body.
(Liver, spleen, fibrous tissue), where it had previously
been destroyed. During times of excess formation, introduction or retention, stored Urine Acid on its way to the kidney would pass through the blood, and would be for some hours in excess of the blood, and would give rise to headaches, and other signs of its presence.

One gram of Urine Acid held back daily for a year, would amount to nearly one ounce in a year.

It is impossible to reproduce all of Feigl's 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.

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**Fig. 1 (p.17)**: Shows the natural + excretion of Urine acid, which occurs in everyone every day. The exact hours in which it will fall depend upon their habits as to food, exercise, sleep etc., 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, one can alter completely the excretion of Uric Acid also throughout the whole day. As a result of this law, acidity in the A.M. and early P.M. hours. Uric Acid is above 3 mg. The normal relation 1:33 is interfered with and comes below 1 for the first time at 3:45 p.m. We must bear in mind however, that this high Uric Acid is dependent on factors. (1) the low acidity of the urine corresponding to the high alkalinity 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 p.m. when also Uric acid is below 3 mg. This fig. serves to illustrate the connection between Uric Acid and Water in excretion, which I have ventured to formulate 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 three. 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 secretion of Uric Acid, Urea Water and acidity in hours. The curves represent the average hourly excretions in each period.
Fig. 2. Daily excretion of Uric Acid in urinome.

<table>
<thead>
<tr>
<th>Time</th>
<th>Uric Acid</th>
<th>Trea</th>
</tr>
</thead>
<tbody>
<tr>
<td>7 AM</td>
<td>15</td>
<td>7.5</td>
</tr>
<tr>
<td>10 AM</td>
<td>10</td>
<td>12.5</td>
</tr>
<tr>
<td>1 PM</td>
<td>7.5</td>
<td>17.5</td>
</tr>
<tr>
<td>4 PM</td>
<td>10</td>
<td>14.5</td>
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<tr>
<td>7 PM</td>
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<td>10 PM</td>
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<td>5</td>
</tr>
<tr>
<td>1 AM</td>
<td>25</td>
<td>3</td>
</tr>
<tr>
<td>4 AM</td>
<td>30</td>
<td>1</td>
</tr>
<tr>
<td>7 AM</td>
<td>35</td>
<td>0</td>
</tr>
</tbody>
</table>

We see that in the hours 7 AM to 11 PM (i.e., the usual working-day hours), Uric Acid is above normal, and water is low. Acidity is also low, and this is the Cause of the high Uric Acid. In the hours 11 PM to 1 AM, acidity and urea have risen considerably. As a result of the high acidity, Uric Acid has fallen considerably below normal, 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 relax, and as a result of these relaxed vessels in the kidneys, they have been a free elimination of water from the blood, and a diminuio

Since the urinary water is as we see very high.

In the hours 1 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 retention 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 Trea. 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 secreted 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.

Sting 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, that it 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 there 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. Activity may be controlled by giving activities by increase or diminution of activity and perspiration
Fig. 4: Showing Yearly occurrence of $	ext{Uni Acid}$ from month to month. Natural fluctuations must be taken into account by offsets, etc.
Figure 3. Daily record of urine fluid 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 Xanthine 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 of the working day, but it was obviously impossible to divide the night without interfering as 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. The 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.

A fair point out that by influencing the solubility of Uric Acid, he could do almost anything he liked with its excretion. But by controlling
The amount introduced into the body, I could
mercury still further, and still more decided
central 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
the excretion of Uric Acid. (1) Those that increase excretion
are: Alkalis, Salicylic Acid, and its Compounds.
Nalcinin, Salol, Phosphates of Soda, Piperazine
Oxinate, Belladonna.

Speaking generally, and apart from the action of
other substances, 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.

The chief substances which decrease the excretion of
Copex, Ipecac, 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
The nitrites. Some Hyposulphites. Iodochloric &c.
All these substances diminish excretion of
Uric acid, and bring about its retention and accumulation
in the body. They clear the 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 urate out of the circulation into the joints and fibrous tissues—where its arrival may be evidenced by prickly and shooting pains—also into the liver, spleen, and other organs.

He concludes (p. 105): The explanation that these substances act on the circulation by their effect on the heart or vessels, or both, or by influencing certain nerve centres, in the brain or cord.

He says with reference to Opium (p. 105): "To say, for instance, that small doses of Opium in producing mental stimulation and well-being act directly on the vessels or nerve tissue is almost to talk nonsense, and make two causes for one effect, when one will suffice. Opium as I have shown cleans the blood of urea, 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. 114-115, he sums up his position in 9 propositions which are too lengthy to quote.

Thiou Acid and Metabolism (p. 126).

Perhaps the most striking feature of originality is the metabolic changes in which others have looked for the cause and origin of Thiou Acid are attributed by Ehrlich to the action of Thiou Acid itself. As an instance of the influence of Thieu Acid on the general metabolism he says: Thieu 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 Thiou Acid), but the effect of an excess of Thiou 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 lesserened formation of Urea urea, and 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 urine is available for solution, more and more marked urea, acetate acidemia, and thus depression of mind, body, and metabolism gets worse and worse. And there seems to be no end to it.

But for drug be given which clears the blood of Urea Acid. The process may be quickly and completely reversed. "Up goes the formation of Urea and special, a steady and progressive metabolism is started and the blood is kept clear of Urea Acid. That is the answer to the question. Why does a very minute dose of nitrate, a few grains of salicylate, or a small portion of a grain of bicarbonate, relieve the articulations all over the body, and cure headache, mental depression?"

He sums up the chapter on Metabolism as follows:

"Urea Acid acts as a toxin in the causation of disease. As a direct local irritant, when it is present in any tissue, in considerable quantity and probably still in solution..."
(2) The continued spasm of the 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 chylo-pneumatic circulations.

We should see that by this action on the circulation it controls the physiology of everyday life and determines the slow or quick Conduction of the human body, just as shutting or opening the flues determines that of the kitchen fire.

Pulse Tension.

He quotes Living's statement (Meggin p. 329) that several observers have noted that the pulse during an attack of Meggin is slow and of high tension. He had already determined that this Headache was due to Throat Acid. By influence, which he could remove the headache and when the amount of Throat 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 Throat Acid that is circulating in the blood." with the idea that "in so far as it depended on Throat Acid it was in my power to alter it in either direction."

Throat 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
Marsy's Law. But pulse rate varies inversely as arterial tension. Thus he says: "(Le cœur bat d'autant plus fréquemment qu'il éprouve moins de peine à se remplir.) The heart assumes more frequency as it experiences less difficulty in employing itself and then he goes on to explain that the chief obstacle to the heart's systole is the resistance "(Que le sang éprouve à se répandre des artères dans les veines et travers des petits vaisseaux) that the blood experiences in gliding (flouage) from the arteries into the veins through the little vessels. And again he says: "(La vitesse du sang augmenté; si la force du cœur augmentée ou si la résistance des petits vaisseaux diminuée)."

The speed of the blood increases if the force of the heart increases or if the resistance of the arteries diminishes.

And then he expresses the effect of the arterial tension "produced" by the resistance in these little vessels on the rate of the heart's action by saying

"Le cœur précipite ses battements à mesure que l'obstacle artériel de la part moins de résistance" (The heart quickens its beating in proportion as the arterial tension causes less obstacle (opposition) to it).

Thus with the signs of high arterial tension he mentions "palpitations rares: le cœur se vide difficilement, la punctation du sang dans les artères est lente, le chérotisme n'a que peu d'amplitude (une-again), le recourbement des petits vaisseaux, comme première de cette tension élevée, des artères se traduit par la diminution du
volume, of extremities; for the monopod coloration of the pigment, for the elevation of the temperature peripherique. (Circulation des Légers pp 315-316.)

(Translation) Infrequent pulsations, the heart emptied itself with difficulty; the flow of the blood into the arteries is slow; elevation is only gradual complicated. The contraction of the arteries, primitive cause of this raised tension of the arteries, is manifested by the decreased volume of the extremities, by the lessened centralising of the heart, 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.

He finds confirmation for his theory in what Sir T. Roberts (Luminary Annual Dinner, p. 71) calls the alkaline tide. In the morning from 6 to 7 am to 2 to 3 pm, in which the quantity of Uric Acid secreted is almost as large as at other times of the day, and maintains his Fig. 3. Illustrates this - that Uric Acid is in excess in the blood daily from 4 to 5 am to about 2 pm, and that it is more or less completely absorbed from it, from 2 pm to midnight. Also, that by altering the acidity of the urine, i.e., the alkalinity of the blood, - say by a few doses of citric Acid, we can completely prevent the urine from being poured out of the Uric Acid in the morning hours. Similarly, a few doses of

From the above statement and the previous
Tension varies with the amount of Tonic Acid that is circulating in the blood. and arterial tension controls the rate of the Heart's action (Marcey). Therefore the pulse ought to be of higher tension and therefore slower in the early AM hours, and up to about 2pm, and of lower tension and therefore quicker in the PM hours, and up to midnight.

He quotes Marcey in Confirmation: "(Circulation du Sang, p.350) On observe le matin au reveil, un reddentionnent du pouls, avec tous les caracteres de la forte tension: le soir au Coucher, le pouls s'accélère et prend tous les caracteres de la faible tension.) The notice in the morning on waking up 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 Bichacys as is shown by Fig. 3 and almost all the other curves he gives, which show that the urine is secreted in the AM hours, and up to 2 or 3 pm, and less the urine in the PM hours which follows.

Since paralyzing the central cord of the Vagus causes contraction of the Renal Vessels, and consequent stoppage of the flow of urine (Brit Med.Journ, Edinb p.104 1895), therefore contraction of the renal vessels diminishes the flow of urine, and dilatation increases it. Therefore physiological contraction is greatest in the hours in
which Uric Acid must exceeds its normal relation to urea and conversely. The shows (p. 144)

That the arteriolar and capillaries are contracted by the Uric Acid in the blood, is completely demonstrated Fig. 3. But 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 Professor Brunton's experiments with the administration of Digitalis and Erythrophleum, 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 occurs (Brunton, Pharmacology, p. 386, p. 530). Prof. Brunton's figure (p. 132) is very instructive for it shows that in the case of Digitalis and drugs of similar action, the diuresis has even wrongly credited to rise of pressure which Prof. Brunton's figure and facts show, but 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.

Next he claims that the course of events in the experiments with Erythrophleum and Digitalis are exactly parallel with what occurs in the
This acid headache, Epilepsy, Hysteria, and other conditions accompanied by high-tension pulse and contracted arteries.

He maintains that what happens in the headaches during plus existence of this Acid in the blood, might apply word for word, to the secretion of water from the lungs, where arteries and Capillaries, "are to being Contracted, in exactly the same way, and in exactly the same relation, to the secretion of this Acid" (p 145).

He next considers how excess of this Acid in the blood, produces contraction of arteries and Capillaries throughout the body, and thinks there are possibilities.

1. This acid may act as erythroplacemum and Digitalis do, in the vessels of an artificial respiration, as the case of erythroplacemum after division of the cord, so that all question going action on the Vaso-motor centre is removed.

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

3. It gives an explanation (as he thinks), but Roberts suggests it also. This acid in a cellular form may block arteries 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 arteries on the one hand and acids on the other (p 147). Roberts (Cromani 1892.) says of the possibility of deleterious precipitation. "In Man and Mammals, the production of this..."
And is all too small to furnish, under any circumstances, a solution sufficiently concentrated to throw down the water in the gelatinous form. In all my experiments on the behaviour of Thrice Acid with blood serum and glycemia I have never seen the least indication of precipitation except of the far less soluble crystalline bodies.

I shall next proceed to show how the various drugs which cleanse the blood of Thrice Acid act beneficially. By insisting that cleaning the blood of Thrice Acid means freeing the circulation and quietening combustion and metabolism throughout the body, affecting above and at the same time, such different organs and tissues as the skin brain lungs stomach intestines.

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

He considers that his proposition that Thrice Acid acts on the arterioles as above stated by contracting 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 acid excreted along with it.

Any one can convince himself of this fact who will take the trouble to estimate excretion for a few days and he will explain the sequence of phenomena thus:

An excess of uric acid over three in the urine comes from an excess of uric acid in the blood. And an excess of uric acid in the blood contracts the arterioles, and diminishes the excretion of water, just as we have seen that ergotism and clysphlebism do. Therefore contraction of arterioles or obstruction of capillaries is directly as the uric acid in the blood, and remembering Harvey's law pulse-rate is inversely as arterial tension, therefore pulse-rate is inversely as the uric acid in the blood.

The mechanism next. That the contraction of arterioles or blocking of capillaries is a mere mechanical action is a fair 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 irritations is there in the AM. and early from hours, which is absent in the
laten 6M hours. or why does a dose of calomel effect the blood pressure at any time? (I am not sure which 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. He not only finds evidence of the theory but is due to true acid.

The evidences of high blood pressure are (2176) "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 pressure of 3 fingers feels full between the beats and the pulse gives a leaping as in fig 37 where the first sound of the heart is long. and the 2nd sound broad 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 under. 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 secretion of urine and in the urine with which they do this. Lower the blood pressure.
Quickly the pulse, and free the circulation throughout the body. Metals and their salts, which form insoluble compounds, with Turi Acid will do this best. But these only clean the Turi 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 to ten days. To carry off the stores of Turi Acid insomuch that the circulation is free, or a course of acids and salicylates greater ultimately.

Histogenous Theories.

Theories of a Primary Pneumatic tissue change.

These deal with the link which must exist between the structural and chemical pathology of Turi Acid manifestation. No one has as yet fully succeeded in explaining this. Though these theories which attempt to define the connexion between tissues and their juices and their mutual behavoir deserve special attention especially valuable in this connection was the suggestion of Leycester that "Turi Acid was not superfluous, always articulate, to cure always combined with joint tumbly and that reproduction of Turi Acid in the tissues rather than in the blood was characteristic of Cauter."
Theory of Parkes and of Barclay

A. Primary alteration in the metabolism of the blood and of the tissues

Parkes (On Urine 1860). While admitting that the kidney was responsible for the retention of Uric Acid, he recognized a retarding influence in "important changes in the metabolism (metabolism?) in the blood or in the tissues. The abnormal products which might be capable of holding back Uric Acid and other substances such as Phosphoric Acid.

Barclay (On Eros and Rheumatism in relation to diseases of the heart 1865). attributed the failure of the kidney to excrete Uric Acid to "a primary change in the blood corpuscles directly due to a fatty diet till each cell after cell became affected and the fatty 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 affected in the origin of the cure, just as its companion the leucocyte is regarded in other theories.

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

Theories of Ord. and Obstein

Antecedent structural changes connected with the chemical changes

Ord. (St Thomas Hospital Reports 1872) considers the priming point which leads to the deposit of Uric Acid to be some essential defect inherited or acquired in the fibrous tissues. He also admits that the nervous
System. Plays an essential part in bringing about the deposit, more especially in the propagation of the guilty inflammation from part to part. When the guilty pustule exists, any sudden excitement of the nervous system can produce guilty inflammation in a violent form and in several parts at one time. He considers this to be "a mode of decay of the whole system, that the deposit operates in the receptor 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."

Obstetric Theory.

falls naturally close into this division. It has attracted a good deal of attention since may judge by the number of times she is quoted throughout the literature of the subject, and his work. "Die Klinik und Behandlung der Gicht" has been translated into French and mentioned with approbation by Chauvel.

As we have mentioned already, he considers this and performed in three parts of the body, which normally take no part in the formation: (1) pustular, (2) phosphoric, (3) muscular 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 par neutral urate. This acts as a
Chimnical reaction in the tissues setting up neuro-biotic changes. Such necrotic areas act as "foreign, reactive irritation in the surrounding parts," and thus cause the phenomenon of the inflammation of a certain attack. The Thure 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 Thure 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 suffused to be generated by the necrosed tissues, after the reaction has been changed from alkaline to acid by the necrosis. We have already mentioned the following underlying this experiment, and would note further, that as shown by the experiments of Tobergen, the Thure Acid is formed in all tissues, especially in those abundant in cellular elements, and further that neutral urates cannot exist, as shown by Robert. Because they can only be produced in the presence of Carotid alkalies, and in the absence of Combust Acid and the Carbinates. We note his that Thure acid is formed in abnormal localities in an assumption no matter what experiments are made. The basis of the theory is assumed not proved.
derivation of Uracil; formerly hinted at by Bouchard and by Purkyné, and taught more definitely by Ord. did not reach maturity until Prof. Guthrie worked out a chemical explanation of the process, and Spallanzani demonstrated the steps in the transformation of Nuclein into Uracil Acid.

Nervous Theories of Gout:

Stall (1782) was the first to advocate a Nervous Theory of Gout. Sir Cullen (?1784) considered Gout as "manifestly an affection of the Nervous system," and asserted that "Gout is more indicative of Nervous disorder than any other symptom." Herivel (1847) thought the origin of the condition would probably be found in the central nervous system. Prof. Cavalleri (1849) favoured a Nervous-humoral theory, teaching that the defective elimination of Uracil Acid was due to some more distant cause. This formed suggestive analogies in the check to the renal function induced by shock, emotion, hysteria. Dr. Leunig (1875) suspected a nervous origin in Gout from the paraesthesia and periodic features of the attacks. But the most dauntless champion of the theory that irritable manifestations are a Tropho-Nervous is Dr. J. Duckworth (A Treatise on Gout 1884).

He boldly affirms at the outset in his book, "No Uracil Acid No Gout." and that whatever be the cause sustained as to the whole pathogenicity of Gout, it was discovered by Dr. J. Duckworth. Cannot he
set aside. He questions whether the thid theory of excess of Uric Acid is sufficient to account for all the phenomena of gout. He quotes with approval Crichton'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 owes a nervous as well as humoral pathalogy. (op cit p. 27). It is something beyond the remnant effects of the abnormal relation of Uric Acid (p. 27).

He regards Gout as a hereditary Neurosis. Habitual or prolonged excess develops hereditary tendency. He defines a Neurosis as a "tendancy to a disposition of tendency on the part of nervous system, or some definite habit of it toward modified evolution or manifestation of Nerve function". and sees nothing more absurd in a man inheriting a certain nervous physiogony than in inheriting a Roman Nose. (p. 27) .

In upholding the nervous factor in gout he permits to nervous features which are characteristic of Nervous affections or Neuroses. Epilepsy, Anguini pedes, Asthma Nervosum, and syncope may be mentioned. The "nervousness of the skin" in the early morning hours alternates with manifestation and disappearance of redness induced by Nerve excitation or depression.

He is not prepared to accept any purely physical views, nor any purely chemical theory adequate to a really comprehensive views. The marked determining influence of the nervous factor is necessary (op cit p. 49).
Ours belongs to the Neurotic type may be either primary or central or may be secondary or induced and he alleges. Case presents many of the characteristics peculiar to the Neuroses, e.g., heredity, periodicity, irritability, and all the manifestations as: taut and perpetual, taut and diabetes, and susceptibility to be induced by nervous changes. Conditions Primary Nervine he regards as a diabetic Neurosis, but he finds it not so easy to account for faint occurring where there is no Neurotic element.

He assumes that at least in some of these a condition of delirium and hypervisio is set up as a result of high living and that the consequent hypersemia of the blood attacks all the Nerve Centres in 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 faints attack become developed. He thinks that one-sided manifestations of arthritis which have been well established in certain cases as joint affections hemorhagic neuroleptic. Indicate still further a dominating Nervine influence. (P. 249)

"Faint is a hereditary Neurosis. Habitual and prolonged excess. develops hereditary tendency. Thirsty mental labor. alcoholic intemperance, debauchery, and other indulged. such propensities in the parent. come to be developed into a definite Neurotic faint. and tendency in the offspring. Therefore Faint appears as a diabetic Neurosis." (P. 249)
But here are other indications besides humidity and periodicity, which seem to indicate a Neural factor in Gout and ally it with the neurones, such as the sudden occurrence of the attacks, the preceding elevation of tension, the time of attack, and the phenomenon character. The connection of the disease with other well recognized neurones, 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 J. Hooker refers to Cammack's. The humoral and Nervous elements in his theory. He says: "I cannot divorce the two ideas, and hence I affirm that Gout is a Neur-o-humoral disease. No whole in health is that acid met with as such... The presence in tissue or secretion is a sign of disease..." Still he looks beyond the chemical pathology of Gout, for a "presiding nervous element" and he finds it in the neurones, which may be either implanted that is primarily impressed as an individual heritable feature or secondarily induced owing to some hereditary condition.

Sir Willoughby Wades Neural Theory.

According to this theory, Gout is rather a neuritis than a Neuritis. He finds patchy areas of acute tenderness over an inflamed joint which involve themselves into narrow lines of acute tenderness, in some cases extending beyond the zone of swelling and inflammation... and which
Can frequently be recognized as following the lines of distribution of Cuthbert 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 neuritis, of which there are two kinds: implicating respectively the conducting grey matter and the protective coverings along the lines of extension, more commonly the upward extension as in Neuritis ascendant, the influence sometimes travelling up as far as the cord itself, and sometimes a downward extension as in Neuritis descendens.

The pathological factor is an (assumed) alteration of the metabolism of proteins resulting in the formation of Diaminurate 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 liquors. By this faulty blood state the elasticity of the nerve trunk is impaired and they are less open to influences which would be insupportable in healthy nerves.

From a consideration of the foregoing theories we may safely say, that practically in D. Duckworth's opinions "No Acid and No Caut" has been accepted by the profession as expressive of the cause of Caut. Though many attempts
views are held as to its origin, physiology and pathology.
We now proceed to inquire about the causes in the body and what are the conditions under which it remains physiological and what are the factors which cause it to render it pathological.

Etiology of Uric Acid.

Mach. (Archiv für inner Pathol. no. 7, 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, while 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 Uric.

By regulating the vessels of the Liver and fasting, no change in the production and formation of Uric Acid is found. Uric Acid was not formed in the Liver.

Shore showed that in every individual, after the 13th hour of fasting, the excretion of Uric Acid remains almost constant. But after a meal, the excretion of Uric acid rises rapidly and sinks again after several hours. The amount of Uric acid excreted does not begin to rise till later, and attains its maximum nine hours after the meal.
and thus falls again; therefore he concludes that then
is formed from the albumens introduced in the form of
food, but that Uric Acetic 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.

Horracewski. (Beiträge zur Rinnisse der
Kamische und der Kamische Banen, Sitzungsberichte

and his pupils show that Uric Acid as well
as Riemine and Hypoxanthin can be prepared from
the tissues, and with especial facility from the Spleen.
This had been stated long before by Parkes (Smeel 1873, 447)
who suggested that Uric Acetic and there 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 there 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 exhaustion or hyperemia.
which reaches its maximum about 5 hours after taking 
good after which it returns to its normal bulk. It should 
be remembered that this enlargement corresponds in time to 
the menstrual conglobation and increased urea excretion 
eventually to be mentioned.

"When fresh spleen-pulp is pulsed down (viscera) the urine acid 
with 8 to 10 times the amount of distilled water, and the 
mixture kept 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 evaporating the undissolved 
portion, and precipitating with Lead Acetate, the albuminous 
substances are removed, and the fluid sterilized. Nitrogenous 
substances are now found in the solution and appear to be 
forerunners of Urine Acid as well as of Cauhlini and 
Hypoxanthine, 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 concened by evaporation 
to a small volume, Cauhlini and Hypoxanthine but no 
Urine Acid are found in it. Guanin and Telinin, which 
former investigators have prepared from spleen pulp.
were not found in the solution. Because by the decomposition
Adrenalin is transformed into Hypoanurin and Guanin into Trianurin.

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

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 Naphthine and
Hypoanurin or into Uric Acid. When however Naphthine bases are formed,
no further oxidation into Uric Acid is possible.

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

It had formerly been supposed that this mother substance
was the nucleus of the lymphatic Constituents of the spleen
and Noltegowski 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 nuclei was suspended was shaken up with either
The nuclei settled on the top of the muddy 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 nuclei. - Horbuzewski was able to prepare Urin Acid by dissolving this nuclei in a very weak lye and treating it with blood at 40° C.

As the nuclei 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 Urin Acid arising from the nuclei by comparing it with the quantity of Urin Acid obtained from the same quantity of spleen pulp alone.

Further experiments showed how far Urin Acid could be obtained from other organs and tissues. Jadownik and Tomschuk

Horbuzewski'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 Urin Acid was present in almost all the tissues of the body in mucous membrane of the bronchi, bone-marrow, thymus, liver, muscles, 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 Urin Acid, and if at only in traces.

As all the tissues corresponded to the spleen in the preparation of Urin Acid, and as either the Karkhin bases or Urin Acid could at will be prepared from them it can no longer be doubted that in the case of these organs also the nuclei contained in the cells is the mother substance.

Accordingly Horbuzewski and his pupils having shown that inside the system Urin 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 F. Kupferwski first investigated how nuclein acted when it was introduced into the body. The investigation showed that the excretion of thiourea could 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 0.75 gm. was injected subcutaneously into a rabbit and in the place of the normal 7-8 milligrams it excreted 20-5 milligrams of thiourea in 24 hours.

A man was fed during the experiment for 5 days on a regulated diet consisting of flesh, bread, butter &c. and the production of thiourea reached 0.689 to 0.861 grams per day. Ten grams of nuclein were then given to him daily in addition to his food, and the thiourea rose to 1 gram.

The day after taking the nuclein it was 0.957 gram and again gradually diminished. In this case there was only a very considerable increase. It is more striking when the nuclein is administered during fasting. In this case the excretion of thiourea falls. During the first twelve hours, one the maximum was 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 gms of Nuclein suspended in water. The amount of Uric Acid and the total amount of nitrogen were estimated every 2 hours, and the results will be seen from the following Table.

<table>
<thead>
<tr>
<th>Hours</th>
<th>Amount of Uric Acid</th>
<th>Amount of Nitrogen</th>
<th>Uric Acid</th>
</tr>
</thead>
<tbody>
<tr>
<td>9-11</td>
<td>81 cc</td>
<td>1.065 gms</td>
<td>46.8</td>
</tr>
<tr>
<td>11-13</td>
<td>670 cc</td>
<td>1.040 gms</td>
<td>46.9</td>
</tr>
<tr>
<td>1-3</td>
<td>338 cc</td>
<td>1.013 gms</td>
<td>67.7</td>
</tr>
<tr>
<td>3-5</td>
<td>148 cc</td>
<td>1.096 gms</td>
<td>93.6</td>
</tr>
</tbody>
</table>

A second experiment gave similar results.

Therefore in administration of nuclein by the mouth, the uric acid excretion is increased. Nuclein is excreted by the slowly digesting residue of Nuclein.

It is most probable, from these experiments, that Uric Acid is formed in man 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 leukocytes which are present in the blood, lymph, connective tissue, glands, in short everywhere in the body. For example (corresponding to the alkaline side of Collets), I am able to cause a considerable increase in the number of leukocytes 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 nucleoli contained in
there converted into Kastrin bases, or Uric Acid within the Cystin. This hypothesis is also supported by the fact demonstrated by many observers that a temporary or permanent leukocytosis is always accompanied by a corresponding increase in the amount of Uric Acid (or Kastrin bases) formed in the body.

In childhood the blood is richer in leukocytes 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 its first day of life, 1-5% of the total nitrogen eliminated, while in adults it is only 1-2 percent.

As already stated, the excretion of Uric Acid in adults is diminished during fasting and rises after taking food especially flesh food. The leukocytes of the white corpuscle correspond to this, their number tending to a minimum after 18 hours fasting, where they remain, if fasting is continued. And then again rising considerably 24 hours after amount

According to Wilkins (Hirsch-Vorlesung 1907, p. 125).

The excretion of Uric Acid remains unchanged from the 15th to the 24th hour of fasting, while the absolute amount varies according to the individual. It is a much absorbing largely by fleshfood. 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 then proceeds more slowly reaches 1 maximum 9 hours after food and sinks again more slowly.
Roberts experiment (Edin. Med. Jour. 1860. p. 87-94). determined by experiment that after seven days and 16 hours fasting the urine of a healthy man who had eaten two good meals was strongly acid, yet did not contain much urea acid. From 8-4 hours after food, urine was less acid—sometimes alkaline but contained much more urea acid.

Nabrzewski'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 urea acid. This increase in the number of white blood corpuscles in the blood after a meal is the explanation only by leukocytes being formed in large numbers in the parts of the body and passing out the lymphatic stream into the blood.

<table>
<thead>
<tr>
<th>Individuals examined</th>
<th>During fasting</th>
<th>After taking flesh food</th>
<th>Amount of fluid in C.C.</th>
<th>Total number of white corpuscles</th>
<th>Amount of fluid in C.C.</th>
<th>Total number of white corpuscles</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. 1</td>
<td>45.00</td>
<td>170</td>
<td>59.9</td>
<td>10.34</td>
<td>7250</td>
<td>+61.7%</td>
</tr>
<tr>
<td>No. 2</td>
<td>47.50</td>
<td>50</td>
<td>42.5</td>
<td>64.2</td>
<td>7500</td>
<td>+67.9%</td>
</tr>
<tr>
<td>No. 3</td>
<td>50.02</td>
<td>120</td>
<td>49.6</td>
<td>10.56</td>
<td>7744</td>
<td>+57.8%</td>
</tr>
<tr>
<td>No. 4</td>
<td>99.50</td>
<td>50</td>
<td>57.2</td>
<td>7.56</td>
<td>14900</td>
<td>+49.5%</td>
</tr>
<tr>
<td>No. 5</td>
<td>87.00</td>
<td>100</td>
<td>31.3</td>
<td>443</td>
<td>7700</td>
<td>+35.1%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Individuals examined</th>
<th>During fasting</th>
<th>After taking vegetable food</th>
<th>Amount of fluid in C.C.</th>
<th>Total number of white corpuscles</th>
<th>Amount of fluid in C.C.</th>
<th>Total number of white corpuscles</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. 1</td>
<td>45.00</td>
<td>170</td>
<td>59.9</td>
<td>10.34</td>
<td>5900</td>
<td>+23.3%</td>
</tr>
<tr>
<td>No. 2</td>
<td>47.50</td>
<td>50</td>
<td>42.5</td>
<td>64.2</td>
<td>4900</td>
<td>+3.1%</td>
</tr>
<tr>
<td>No. 3</td>
<td>50.02</td>
<td>120</td>
<td>49.6</td>
<td>10.56</td>
<td>5050</td>
<td>+92.8%</td>
</tr>
<tr>
<td>No. 4</td>
<td>99.50</td>
<td>50</td>
<td>57.2</td>
<td>7.56</td>
<td>5750</td>
<td>+2.5%</td>
</tr>
<tr>
<td>No. 5</td>
<td>87.00</td>
<td>100</td>
<td>31.3</td>
<td>463</td>
<td>5350</td>
<td>+25.5%</td>
</tr>
</tbody>
</table>
I have placed these two tables one under the other to facilitate comparison. The amount of urine acid and number of leucocytes after a mixed (mainly flesh) meal and a meal entirely vegetable, as some claim that the increase in urine acid takes place after a flesh meal only. These tables show that leucocytes and urine 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 urine 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 urine acid is due to leucocytes and not to the diminution of albumen introduced as food in individuals in whom no digestive leucocytes take place or does not matter its appearance till very late. There is no measured excretion of urine acid, as it only appears much later after the meal than usual.

Dr. Schaefer showed by repeating the above experiment on a patient suffering from Anaemia Renalis.

These experiments show that the excretion of urine 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.

In the only with Schaefer's experiments it is that one cannot learn from them how the urine...
current during the whole 24 hours was influenced by the different foods. The experiments of Bleichstein and Schultze (Pflügers Archiv, Bd. 45, p. 401) confirm this deficiency. They determined their own total excretion of urea and urinary acid for 24 hours under a vegetable and under animal diet. Bleichstein's results were

<table>
<thead>
<tr>
<th></th>
<th>Animal Nitrogen</th>
<th>Vegetable Nitrogen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Nitrogen</td>
<td>24.4465</td>
<td>19.8082</td>
</tr>
<tr>
<td>Urea</td>
<td>22.113</td>
<td>9.2432</td>
</tr>
<tr>
<td>Nitrogen in Urine</td>
<td>0.859</td>
<td>0.791</td>
</tr>
<tr>
<td>Urea Acid</td>
<td>0.2763</td>
<td>0.2637</td>
</tr>
</tbody>
</table>


Proportion of nitrogen to nitrogen of Urea Acid: 1: 73.6: 1: 35.05.

Schultze's, whose individual excretion of urea per day was carefully estimated at 31.647 to 33.8549 grms. per day, Acids at 0.826 to 0.9424 grms. reached in successive days on an animal diet.

<table>
<thead>
<tr>
<th></th>
<th>Animal Nitrogen</th>
<th>Vegetable Nitrogen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urea</td>
<td>1.3856</td>
<td>1.270</td>
</tr>
<tr>
<td>Urea Acid</td>
<td>1.3856</td>
<td>1.478</td>
</tr>
</tbody>
</table>

It is abundantly proved by hue and other investigations by Kurethfeld (Mechan. Archiv Bd. 117, p. 201) and Schultze that Urea Acid is formed by the destruction and decomposition of the constituents of the body's processes which are directly influenced by the food. How 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 three secretion rates were almost mathematical accuracy with the amount of proteins taken, the oscillations in the urea acid excreted are much more limited and are not regulated by the diet.

So long as the generally accepted opinion was that the urea acid arose from oxidation of albuminious 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 known as urea acid and the rest as urea. Many writers accepted the existence of such a constant proportion and endeavored to estimate the normal relation. There are some of the last that has arrived at such an estimate. (see under @#Thur go Theory#A). According to Sturm, the normal relation is: "Urea Acid : Total : 1 : 30 or 40."

The experiments of Pflüger and Alberti Schultze would favor his theory, we feel compelled to draw the conclusion from them that the excretion of urea acid in each individual is a fairly constant quantity. Changes in which indicate variations in the metabolism of the body.

Pflüger's proposition that there exists a constant proportion between the excretion of urea acid and the number of white blood corpuscles in the blood gains additional support from the fact that the production of urea acid is increased by a whole series of diseases characterized by the formation and destruction of a large number of corpuscles.
The influence of various disease processes and positions on the production of Uric Acid

Lsche.[1](Klinische Umianstye p35) affirms that in his territory the amount of Uric Acid excreted can rise to 4 gms. in 24 hrs. and that he himself observed an excretion of 3.4 gms. in a case.

Pintels. (Deutsch. Arch. f. Klin. Med. Bd. 37 J. 33), notes a case with daily excretion of 4 gms. of Uric Acid and another case with enormous enlargement of the spleen from which convulsions from the size of a hams and to a pear were passed.

Rodman and Delany. (Pfuijer Archiv 47 p13) formed 1.22 gms. per day and 1.42 gms. on a late examination.

Sticheler (Viehrs Archiv 199 p280) examined the excretion in a healthy person and a Luesyphoric woman and found that in the former the proportion of Uric Acid to Threa. took 1:59, 1:66 and 1:15 33). For the nearly constant for the 2 individuals. He brought down the excretion of Urea: 1.22 to 0 gms. by vegetarian diet while the Uric Acid remained unchanged. 1.91 gms.

On a purely albuminuric diet the Threa rose considerably, but the Uric Acid was not appreciably increased.

While diseases especially Pneumonia are cited by Frahnherowski as being accompanied by Luesyphoria. And measured 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 gms. per day. and a like quantity is said to
Burns

In severe Burns an abundant secretion of Urine Acid takes place. A boy of 15 (Levitsch, p. 35) who had more than 50 per cent of his body burned by Burns, gave off on the 3rd day 0.99 gram of Urine Acid, on the 5th 1.22 grams, on the 7th 1.59 grams, etc., while the total amount of Nitrogen was not unusually large.

Just as these morbid states which are accompanied by an abundant formation and disintegration of leucocytes, are also accompanied by an excessive secretion of Urine Acid, so Hubayevski has found that those drugs and poisons which increase the number of leucocytes in the blood, also increase the secretion of Urine Acid, and that various drugs of an opposite class, which prove of service in seamen's diarrhea, also diminish the Urine Acid secretion. Certain poisons appear to increase the power of Urine Acid. Bartels (St. Archiv f. Klin. Med. p. 652, Levein) noticed this in a case of CO poisoning.

Thermone (Frankel-Rothman) measured the amount of Urine Acid secreted. He also gave for the mammalia.

Quickly brings about a considerable diminution in the leucocytes, on healthy people (Levein, p. 36) was made with the result that one hour after swallowing 10 milligrams of Urine Acid the leucocytes were increased 25 to 3.45%. In some cases after a few hours they were increased as much as 48.7%. Shortly after this marked
Methylene.

The formation of Uric Acid. Dr. Chittenden, professor of physiological chemistry at Yale University, published his results of his experiments on alcohol in "The Dietetic and Hygienic Gazette." (Quoted by the Medical Pioneer, Vol. 1871). 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, whether the total amount of nitrogen in the urine is increased or diminished.

Currie (beard beak week 10.11.11.) found by experimenting on himself, that the excretion of Uric Acid was always increased after puncturing freely of alcohol. A similar phenomenon is given by Barcroft, who also experimented on himself.

Exercise.

Exercise increases the excretion of Uric Acid and brings about the effect is brought forward by Lauremip. 37.

Haw. (op. cit. 280, 284). Recycle exercise for 450 hours.

Currie always increases excretion of Uric Acid in my own experience.

Currie always increases excretion in a healthy person.

Currie, which has already been given once.

After a plentiful meal, consisting largely of flesh, the number of leucocytes in the blood.

Currie showed that increased leucocytosis was brought about by administering Methylene (ante stud. 92).
Grown 5. Incubated in water increased the number
of Leucocytes in all ty of experiments almost 50%.
The patients experimented on had fasted for 18 hours
before the nuclei were administered and took their
first meal 2 1/2 to 3 hours later. The blood cells
from previous sample were counted. The figures being

Conclusions (See p. 28)

1. True acid is formed in the body by the disintegration
of albuminous substances and tissues, especially by the
nuclei or Nucleins.

2. The secretion of True Acid becomes increased or
diminished by all factors (chronic. malignant. fevers).
which give rise to an increased 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 (defensive). This Leucocytosis
probably arising from the nucleus of the food.

4. The amount of True Acid excreted in 24 hours is not
influenced to a great extent by food. This is
however the distinction noticeable. the easily digested
animal albumens. set up digestive Leucocytosis and
formation of True Acid. much quicker than the
vegetable albumens which are difficult to digest.
Urie Acid in the blood, and the form in which it exists physiologically.

Since Urie acid takes such a large part in the physiological and pathological processes of the human body, it seems natural to inquire: 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 Cheminard in 1845, who demonstrated the presence of Urie 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 has been already mentioned. It is demonstrated to every student of medicine at the present day.

In cases of chronic gout, Urie 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. One should remember that there is great excess also of Urie acid in cases of chronic lead poisoning and in certain diseases of the kidney.

Urie acid may be demonstrated in various secretions and fluids of the body, in the urinary tract. It has been demonstrated in the cerebro-spinal fluid, in the intestinal secretions in the effluvia of pleurisy and Pericarditis in the discharge of serum, seroforaneous eruptions, and in the form of dust (Sudanii White) in the skin.

Roberts (Phrenom Edit 1491 837) has demonstrated
had serum can take up uric acid in the proportion of 1 in 500, and that the greater the concentration of the solution in the bread experiment the more marked the deposit of crystals. Leuwer obtained similar results in experimenting with ascitic fluid. His results are quite in accordance with Canning's statement (NATURE of Cancer p. 57) that serum containing 1-2 or more per Nauent parts of uric acid shows abundant deposition of uric acid crystals.

Estimations of the Quantity of Uric Acid in the Blood

Salomon (Chirurg Annalen 1878/1879) found uric acid in the blood of patients suffering from Pericardia and Gouty Arthritis.

Von Talsch (Jahr. der Klinische Redaktion Drummer von Harinander a Harshin Benuch ex B consensus (1891) undertook the investigation of this question with abundant material at his command. Controlling his experiments with a solution of uric acid which he injected into the blood stream. He demonstrated that almost the entire amount of uric acid dissolved in the blood could be estimated. It seems the same (uric acid and ascitic in cancer p.) He says he could recover in the urine almost every portion of uric acid administered to patients (already quoted). (Von.)

He 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. He found uric acid only in one patient's urine. 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 Chronic Kidney and Varicose. 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 oxidized in the blood. By the activity of the Red cells. If the number of these is diminished the Uric Acid remains uncharged, and is stored upon the blood as such.

From the examination of von Tappeiner's table it is evident, that there is an excessive production, and active destruction 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 course of Kidney disease was due, probably, to decreased excretion. Though von Tappeiner explains his results differently from Hulthemerki it is evident from the analysis of his experiments that they are unfavourable to Uric Acid being a product of the tissue metabolism of the body, and derived from the decomposition of Nuclein.

The Chemistry of Uric Acid and its Compounds.

Uric Acid is Uric acid 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. The now
procured to enquire what chemical compounds it forms in the blood. With the base it there meets and unites with.

It is most commonly met with in the human economy as Biurate of soda in gouty tophi, and it was formerly supposed that the uratious deposit formed under certain circumstances in the urine was also this acid urate or Biurate.

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 (Cromwell Lectures 1872) by studying the uratious 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 cutaneous conditions or titling diabetes and is a common accompaniment of Pyramids and of spare wasting annual diseases of all kinds. It is found only in acid urine and is never thrown down in neutral or alkaline urine. It is recognized clinically by disappearing from the urine on heating.
Composed by the microscope it appears granular and has no crystalline structure. It is a representative body, typifying the excretion mode in which nitrogen is eliminated in most 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, \( \text{C}_3 \text{H}_2 \text{N}_4 \text{O}_3 \), and forms neutral and acid salts. Its chemistry was worked out in Liebig's laboratory by Borchardt and Jelfen (an English student), and has been unquestioned since that time.

Neutral Uretates can only be produced in the presence of caustic alkalies and in the absence of Carbonic Acid and its carbonates. Conditions impossible in the living organism. We may therefore dismiss these from further consideration.

**Acid Uretates** or P.Uretates 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 Monium P.Uretates. It has been seen in health as a deposit in unaltered urine. Only when urine undergoes ammoniacal decomposition P.Uretate is deteiled as minute, elongated, chalky bodies.

It is assumed that Uric Acid exists as a true P.Uretate in normal urine, and if introduced into normal urine it decomposes. In none we any proof...
that Biurate are found in healthy blood or intestinal juices. Biurate though known to us as pathological products, in guilty deposits, are not strictly speaking known to us as pathological products constituent, 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 arises, what is the normal and physiological form of combination, which is neither Neutral Urate nor Biurate?

Amorphous Urate: Deposit Examined

Amorphous urates are not found chemically pure in urine. Their most important reactions are marked by the urine. In order to study them, the deposit is filtered, washed with rectified Spirit and dried. Its most characteristic reaction is its peculiar lustrous when heated with pure water; may now be observed. If some of the deposit be placed on a slide under the microscope and distilled water incinated under the cover-glass, the amorphous urate is quickly disintegrated, and large, shaped crystals of Uric Acid take its place. This process continues till all the amorphous urate breaks down and disappears, and in 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 though more slowly, in the urine and
that is why crystals of time acid are always found
in the amorphous sediment of urine which has stood
for so many hours. It is much natural that the "urinary
excretion of Birds and Reptiles displays identifyingly the
same reactions as the Ammonophosphate. When examined
in a fresh condition by the microscope it is found to
contain 9 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 time acid. The difference in
physical form between the two substances is a
more 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-crystalline
anamnestic excretion of Birds and Reptiles are
essentially one and the same substance.

Hawks next asks. What is the constitution
of this substance? Is it merely a mechanical mixture
of time Urate with varying quantities of free time Acid?
or is it a definite Chemical combination representative
of a new or 5th order of time Acid salts differing
essentially from the two regular orders, previously recognized?

P. Bruce James. Published in the \textit{Transactions}
of the Chemical Society, his researches on the Composition of the amorphous deposit, quarrels in healthy urine. He shows that on adding pure water to the amorphous deposit after it has been previously washed with spirit and filtered, but the part of the sediment not dissolved by the water is Thric Acid, and the portion dissolved is pure B. Urate. On analysing some samples of amorphous urate, he found out the proportion of Thric Acid to the quantity of base, he found that the Thric Acid was in excess, of the quantity required to form B. Urate with the base present. The separate analyses gave discordant proportions, but their mean gave a proportion of Thric Acid which was very nearly twice as much as was required to form B. Urate with the sum of the bases. This suggested to James that a third order of Thric Acid exists, more complex in constitution than the neutral and acid urate in which an atom of B. Urate was loosely combined with an additional atom of Thric Acid. He therefore inferred that the amorphous urate deposit consisted of at least often contained such a combination. (Purdz, p. 24.)

From these experiments it is evident, that the amorphous urinary sediment often contains much more Thric Acid than is required to form Acid urate, and that this excess of Thric Acid is as feebly held in combination by the acid urate, that washing with cold water will set free the crystals of Thric Acid. As no combination of this kind was previously known
an attempt was made to form an artificial sediment

"Trinito which when washed with cold water, or sauced

with warm water, would be decomposed into free uric acid or urate.

Then on 1872. 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 heating into uric acid and urate of Potassium. This substance might be considered to resemble the Quadravalent of Potass, which differs from the Acid urate, by containing double the amount of uric acid, and following this nomenclature it may be called the Quadravalent of Potass."

Why the deposit should assume this form is stated by Heintz (J. Pharm. 1821 p. 467) who says: "To help heat among the urates of which the deposit consists, whereof urate of urine is present, which is shown to always precipitated an opaque dross which he states is always precipitated an opaque amorphous "dross". He says: "(amorphous) but for the formation of this fine boring amorphous sediment. Some must be formed of Potass or absoct." He then states how he formed his amorphous deposit artificially.

He dissolved free Acid uric of Potass or Laciurum ley.

Acidulited with acetic or phosphoric acid. Till an Amoxic reaction was obtained upon which a dense white precipitate came down. When washed with distilled spirit dried and filtered. This was formed lo Mpess. The characteristic properties of amorphous urate deposits i.e. it was granular not crystalline
in appearance, under the microscope, decomposed by pure water, giving rise to an abundant formation of Thio Acid crystals. On analysis this compound was found to consist of four equivalents of Thio 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 its theoretical formula, of Dassim (mixture) Bi-urate and that the Thio Acid that remained undissolved approximated in amount to that which went into solution as Bi-urate.

The general formula for the compounds so far as they might be termed would be $\text{H}_2\text{C}_5\text{H}_4\text{N}_2\text{O}_3$. MHT. ($\text{C}_5\text{H}_4\text{N}_2\text{O}_3$). Bi-urate simply $\text{H}_2\text{FeMHT}$.

But since James' results did not come out quite accurately in accordance with theory.

The quantity of Thio Acid dissolved and by water should have equalled the quantity retained in solution as Bi-urate. Theory required the proportion 1:1, but the results obtained were 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 Thio Acid crystals has commenced.

While 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 it exist in a third order of the Acid salts differing essentially from the two urates already known, and having a composition corresponding to the hypothetical formula for Quatrururate? In presenting his investigation he made use of the following materials:

1. The amorphous urate deposit of human urine.
2. The urinary excretion of birds and reptiles 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 amount of urates and uric acid in the samples.
2. To proceed by way of what may be termed "Wet analysis" i.e., 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 urates. If the Quatrururate 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 inconsistent in character that no conclusions of any value could be deduced.
from them. The explanation of this lay in the fact that "Ammonium urate as it exists in the urine exists under conditions of change, which tend to progressively liberate the urine 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 thus reliable results could not be obtained from materials processed in this way. He hence devised the following means of obtaining a sufficient supply of the ammonium deposit.

He dissolved successive additions of Potassium or Sodium Bicarbonate in slowly heated urine till it became slightly alkaline. heating the mixture in a flask to 160° C. and shaking it up for a few minutes with excess of pure urine Acid. If this means a large amount of urine Acid was dissolved. While still warm the mixture is drawn 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 a temperature of the hand. A much better result is obtained by dissolving excess of Potassium Acid 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 radiculated crystalline structure, resembling to remembrance the spheres formed in the urinary secretion 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 to near the boiling point, and left standing for 48 hours, when cool the liberated urine 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 urine 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 HCl, then set aside for 48 hours. The precipitated crystals were collected dried and weighed again. The amount of urine acid by Wilsin's method to be, almost exactly equal to that retained in solution as is shown in the following sample experiments.
Table showing the results of Water Analyses of two samples of
Ammonium urate. Solution prepared by the Pot. Acet. method.

<table>
<thead>
<tr>
<th></th>
<th>1st Sample</th>
<th>2nd Sample</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urie Acid separated by water</td>
<td>0.080 grm</td>
<td>0.164 grm</td>
</tr>
<tr>
<td>Urie Acid dissolved in Bi urate</td>
<td>0.077 grm</td>
<td>0.159 grm</td>
</tr>
</tbody>
</table>

These results agree closely with the requirements of the 
Diammonurate Theory.

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

Table III Water analysis of two samples of Rats' urine.

<table>
<thead>
<tr>
<th></th>
<th>1st Sample</th>
<th>2nd Sample</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urie Acid separated by water</td>
<td>0.160 grm</td>
<td>0.126 grm</td>
</tr>
<tr>
<td>Urie Acid dissolved in Bi urate</td>
<td>0.165 grm</td>
<td>0.132 grm</td>
</tr>
</tbody>
</table>

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 unabraded as it came from the kidneys having been 
contaminated by the urine used in cleaning the 
Cages in which the creatures were kept. From the 
following Table it will be seen that the urine of the 
Reptiles when voided consists of Diammonurate mixed 
with a certain proportion of pure Urie Acid.

Table IV Water analysis of four samples of Reptile urine.

<table>
<thead>
<tr>
<th></th>
<th>1st.</th>
<th>2nd.</th>
<th>3rd.</th>
<th>4th.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urie Acid separated by water</td>
<td>0.124 grm</td>
<td>0.110 grm</td>
<td>0.204 grm</td>
<td>0.215 grm</td>
</tr>
<tr>
<td>Urie Acid dissolved in Bi urate</td>
<td>0.117 grm</td>
<td>0.065 grm</td>
<td>0.141 grm</td>
<td>0.140 grm</td>
</tr>
</tbody>
</table>

These developments between the Calculated and obtained 
results, however, disappeared when a comparatively 
small fraction of the urine was obtained, and
Subjected to quantitative analysis.

From these experiments it could also be deduced that the "Compounds of Thurate and Codex which constitutes the amorphous sediment, contains exactly twice as much Thurate as the salt which is soluble in water."

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

Table 7: Water analysis and quantitative analysis.

<table>
<thead>
<tr>
<th>Sample of Potassium Dianhydrurate prepared by the Acetate of Potash method</th>
<th>Water analysis</th>
<th>Quantitative Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water acid separated by water</td>
<td>0.85 gmm</td>
<td>Proportion per cent.</td>
</tr>
<tr>
<td>Thurate acid dissolved as Thurate</td>
<td>0.55 &quot;</td>
<td></td>
</tr>
</tbody>
</table>

Quantitative Analysis

<table>
<thead>
<tr>
<th>Found</th>
<th>Calculated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thurate</td>
<td>0.198 gmm</td>
</tr>
<tr>
<td>Potassium</td>
<td>0.0226 &quot;</td>
</tr>
</tbody>
</table>

The numbers in both these analyses of the Potassium Compound come out with almost perfect exactness, in agreement with the Dianhydrurate theory of preparation. These results were confirmed by the analysis of the corresponding sulphate Compound.

According to these analyses, it is evident that the same sediment which exactly resembles the artificial Dianhydrurate, in appearance, chemical relations etc., has also the same chemical composition and that this is also true of the Compounds of Thurate Acid.
In solution in the urine.

In the same way Roberts succeeded in preparing Quadrinates of Ammonium Calcium Magnesius.

He remarks with regard to the above experiments (p. 26) "The lines of analogy 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 chemical composition corresponding to that of a hypothetical Quadrinate with the general formula $H_2 U \cdot H_2 O$. In deference to the authority of Bruce Tones I propose to adhere to the designation Quadrinate without however pre-judging whether in reality the analogy with Zircononiate be a chemically sound one."

He explains the discrepancies between the results obtained by Scherer and Bruce Tones by showing that the ammonium deposit was apt to be contaminated with Pure Uric Acid or Biturate according as the solution from which it was precipitated was slightly below or at the point of neutrality. He quotes the following experiment in proof of that conclusion (p. 26):

"500 cc. of urine acid urine was divided into 2 equal portions. A and B. Sulpho Perchlorurate was added to A in the proportion of 1:7. The addition produced only a feeble degree of alkaline reaction. 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:

Uric Acid separated by water 97.76%

Uric Acid dissolved as Bi-urate 0.142

The other portion B, was treated with calcium bicarbonate in the proportion of 0.29. This addition rendered the urine freely alkaline. B was then treated exactly like A. The resulting precipitate gave with water analysis:

Uric Acid separated by water 97.89%

Uric Acid dissolved as Bi-urate 0.144

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 emphasizable on the supposition that in one case the quinohydrotaurine was contaminated with free Uric Acid, and in the other, made Bi-urate in an amorphous condition.

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

The materials for a plausible theory can be founded upon the researches of Nordmann 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 third possibility is proved untenable by the experiments of Zuckermann, who showed that uric acid, being formed in the body by increased cellular activity, is quickly excreted in the urine. Thus can there be increased uric acid because in diseases of the heart and lungs, in which uric acid is diminished.

Von Tacke showed that there was no increased proportion of uric acid. He reported that in the blood of cases dying from pneumonia (in which uric acid is deficient), there was generally a great excess of uric acid and 6 cases of this kind gave an average of 0.59 per cent.

Von Tacke: "Ueber Wuricuraminsauren, Deutsch Med. Wochenschrift 1890 Aug.;" he 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 typhus and typhoid fever, he wrote, the blood is mixed with carbonate acid. He wrote: "Ureic Acid 1 Cantoins. Er Wohlekle Blut.

Klinische Beobachtung der Kranken des von Hammeine und Karsinomen von Blute. 1891 p. 96 he says. "So geht jetzt schon aus den Beobachtungen hervor. Unbeschadet der Blut mit Kohlenwasserstoffe ist allmählich bei Verfallen der Blut, u. am Rand von Blutstich unvermuthet fällt häufig zum Auftreten von Hammeine in Blute. (Der preceding sentence is a free rendering of this.)"
Increased production never produces Gout. So long as the Kidneys remain intact functionally.

In 

in which we know there is a great preponderance of White Blood Cells. In the Blood, 3 to 4 gases 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.

The fact that though Uric Acid production is greatest in childhood and yet Gout (arising on 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.

An increase of Uric Acid in the Blood during affections of the Kidneys of various kinds was found by Von Tchek. (op cit. p. 142-3.) In 12 cases of kidney disease, Uric Acid was found in the Blood of 9.

Three 4 were cases of acute nephritis 1 spurious degeneration and 2 of pyuria on kidney. A similar fact in given on p. 97 of "Klinische Redentre". One of the 2 negative cases proves nothing as the amount of blood obtained was too small. The amount of Uric Acid was greatest in cases of abscess of the Kidney and uremic.

None malignant leukemia has been frequently noted by many writers as a Cause of Gout, and the symptoms of Prof. Siiterenden (above narrated) were in every thing. This might be because alcohol by causing fat is indirectly increasing...
tissue metabolism and thus liberating energy stored up in the body, enables a patient to draw upon capital when he cannot upon income. One may be that the excurve are polecal or rather the secretion put up by the kidney sets up a mild nephritis which interferes with the excreting powers of the kidney.

The same explanation may be given of the death 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, Buechegy, Teocund, Allince Carnot. The latter states that one fourth of the cases he treated in hospital in Paris were men whose occupation brought them into close contact with lead—such as painters and plumbers. Carnot found that lead in the blood of patients affected with chronic lead poisoning rose when they showed no symptoms of lead and he believed he could prove that the quantity of this acid excreted in the urine could be diminished by the administration of lead salts in the usual medicinal doses” (Buechegy op cit p 73)

A comparison of the pathological anatomy of the kidneys in commencing fatty 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 Gaunt, 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 secretion of urine acid is lessened.

In Byerly Buckworth it is among九 cases of chronic lead poisoning and one-fourth suffered from chronic nephritis. Note that at its beginning the kidney disorder need quite rise to very few anatomical changes as the primary cause is the decrease in the secretory power of the kidney by which urine acid alone or in combination with other constituents of the urine is less easily eliminated. The commencing necroses of the kidney for secretion has been noted by Charcot who reports that certain odoriferous bodies such as indurative cannot pass off the urine in early Gaunt.

Hepatitis considered the second possibility with

(2) That urine be formed in normal quantity and fail to be excreted probably through defect with kidney.

With respect to the above conception of the pathogenesis of Gaunt, it is 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 gains a plausible explanation of death both in poor and badly nourished subjects and the rich and non-vivants. They of the enigmatic Court of Leuk 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 Stieglitz, it is formed in the body by the disintegration of the albuminoid substances of the tissues especially of the muscle 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 leukocytes. That there is a temporary plus leukocytes immediately after taking food and especially flesh food, due most probably to the nuclei of the ingested food. We have shown also from the experiments of von Takuschn 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 Dendritic, etc. of sodium, potassium, calcium, magnesium, etc.

Within the body it is formed as a Bi-urate or 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 is 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, thin forms, or clusters.

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. Needless to say the toxic theory of its action upon nerve and muscle tissue can be shown to be true.

When we reach this stage of our inquiry, 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 Dicarburate, and that any departure from this condition must be regarded as pathological.

We shall later quote his experiments which show that Dicarburate in the urine breaks up into free uric acid, known as Brevet, and uric acid. We now propose to show from his experiments the converse changes which the Dicarburate 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 urate conjugates 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 Biturate in water.

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

(b) In serum, sodium biturate was found to be soluble in the proportion of one part in 12,000 and the following experiment is very instructive. A metatarsal bone of a guinea pig, 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 away in a few days.

(c) In glycine. This behaved exactly as serum, only minute traces went into solution. The cause of this inability of blood serum and glycine to dissolve the acid used in Campomeds was shown by experiment to be dependent on their albuminous constituents and in no way upon their albuminous constituent. Serum deprived of its albuminous constituents, dissolved the acid and its compounds as completely as distilled water had done.

Sodium and its derivatives glymph and glycine, though differing from each other in their albuminous elements, are almost identical as regards their solubel 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 1 (Roberts 1902, p. 275) showing the percentage of the several salts in blood serum.

<table>
<thead>
<tr>
<th>Salts</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium Chloride</td>
<td>50%</td>
</tr>
<tr>
<td>Sodium Bicarbonate</td>
<td>20%</td>
</tr>
<tr>
<td>Sodium Sulfate</td>
<td>10%</td>
</tr>
<tr>
<td>Sodium Phosphate</td>
<td>0.5%</td>
</tr>
<tr>
<td>Potassium Sulfate</td>
<td>0.6%</td>
</tr>
<tr>
<td>Calcium Sulfate</td>
<td></td>
</tr>
<tr>
<td>Magnesium Sulfate</td>
<td>0.5%</td>
</tr>
</tbody>
</table>

This suggested to Roberts to study, after the method adopted by Prince Jones, the chemistry of urine precipitation by means of an artificial solution imitating closely the composition of serum as regards its salts. A glance at the above table shows, that the saline basis of serum consists of Sodium Bicarbonate, and Sodium Chloride to largely as they preponderate. Roberts found experimentally that a solution composed of the above salts in the proportion shown in the Table would react with urine acid and the urine in the same manner as blood serum itself. He called this the standard solution or standard solution and with it he subjected urine acid and the urine 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 form
they behaved exactly as with serum. Only the smallest
traces of Bi-Urate were taken up by it at 100°F.
Its saline substances are very largely employed
in the treatment of Gout, the value of such
determinations of their effects on the solubility
of Urate is obvious.

Sodium.
The Bi-carbonate, Chloride, Sulphate, Phosphate and
Salicylate all diminished the solvent power of
the medium (io hastened precipitation) and the
alkaline or neutral had, not the slightest
influence on the result.

Potassium.
Salt's exercised no influence neither for nor against
the solubility of the Bi-Urate.

Calcium, Magnesium and Zinc Uminate salts diminished the
solvent power of the medium on Bi-Urate.

Summary of the Results obtained by Roberts (1882).

(a) The influence you start depends exclusively on
the nature of the base, and has no reference to
the Acid radical 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 calcium exercise a strong deterrent
influence, and its deterrent influence increases
with the increasing per centage of the salt in solution. Salts of Calcium Magnesium and Ammonium have also a deterrent effect, but slighter than the salt of Sodium.

Behavior 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 here. 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 dependent on the salt 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 the acid is digested with steam, a synoid or a 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 nitric acid. A solution of sodium bicarbonate alone has as much solvent power on nitric acid as when it is a constituent of these media along with sodium chloride. The question now arises: What is the combination in which the acid enters into solution? It cannot be the nitrate, for it is almost insoluble in these media. The neutral nitrate, for it cannot exist in the presence of the carbonates. There is only one conjecture left: very well I come into solution as a quadririate, and we must have more solid ground to stand on than merely conjecture.

If the acid were dissolved in standard solutions and evaporated to dryness, the resultant residue was always a nitrate. The reason being that as evaporation proceeded, the solution gradually became more rich in base (\[SO_4^{2-}\]) and therefore more potent to change to quadriruate (assuming for the present what we shall afterwards demonstrate).
Roberts made many attempts to throw down a Quadrinurrate from the solution but always failed till he took advantage of the different solubility of Quadrinurrate at different temperatures. By the following experiment (op. cit. p. 85) he succeeded in forming that Urni Acid passes into solution in the presence of alkaline Carbonates as a Quadrinurate.

"When Acid in excess was digested with blood heat, in a one per cent. solution of Sodium Bicarbonate under constant agitation for 20 minutes. The filtered product was rapidly cooled on ice. It here 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 Quadrinurate, that is to say it was decomposed by water with abundant emission of Urni Acid crystals. A corresponding experiment with a 5° solution of Potassium Bicarbonate yielded exactly the same results.

From the above experiment it is evident, that when Urni Acid comes into contact with blood, serum or any standard solvent it enters into solution in the first instance as a Quadrinurate. But the process does not stop here. The Quadrinurate gradually takes up another atom of one and is thusly converted into "Biurate" which is by any precipitated on 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 20 cc of the standard solvent. The flask was tightly corked and placed in a 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 liquor. Things remained apparently unchanged until the evening of the second day. When a few drops of Bi-Urate were detected among the undissolved sediment of Uric Acid. On the third day however a marked change was observed to be taking place, consisting in an abundant precipitation of fibers and tufts and detached needles of Bi-Urate.

On the fourth day the precipitation appeared to be nearly complete for the supernatant liquor now showed only small traces of Uric Acid, when it was treated with Hydrochloric Acid.

In 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 unsolved. It was placed in a coated phial in the warm chamber. It remained mummied 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 liquor was found on accedulation to contain only traces of Uric Acid.

Reddick 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 Ptyal disease. In the Ptyal 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 Child' is declared. Then follows a process of recovery, with restoration of the blood to a pure state. That is, with a renewed impregnation of Uric Acid. In the artificial counterfeet we observe a similar succession of events, firstly, impregnation of the medium with Sodium Bi-urate. Secondly a period of incubation or maturation during which the Bi-urate passes.
reaction of uric acid with synovia.

It is a matter of common observation that urate deposits choose as their seat of aggregation 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 untrammeled 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 one, he experimented. He found that when these media were incubated with uric acid to an equal degree, precipitation of 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 uric acid deposits 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 Ord, in the course of his researches on the influence of carbonic upon crystalline form and cohesion. It is of great interest in the present inquiry 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. Hare mentions this gelatinous form (April 3589) 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 digitalsin a thrombosis locally in the blood vessels and raise the blood pressure. (1) By contracting the muscular tissue of their walls. (2) It may act directly on and through the Vaso motor centre. (3) It may act by mechanically obstructing the capillaries. He states that 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 (cutaneous) Unity 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 lodge 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 Unity Acid phenomena, as the Rheumatic group, and also to Chronic Bright, Dyspepsia, Post-paralytic Conditions, and Menstruation. He also thinks Thrombosis (op. cit. p. 389) may in some cases be explained by this cutaneous 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 Thunet, while Quadrinate is passing into the Thunet Condition in the blood, might constitute a fixed nucleus which clotting might take place, and that the Thrombosis not infrequently observed in County cases might thus be accounted for (p. 398). Roberts is of opinion that the quotations.
forms of Urni Acid is not a true colloaid, because it passes with ease and unchanged through a dialysing bag that it is a hydrated form just as the crystalline Bz Metals are an amorphous form.

Formation of the Gelatinous form of Urni Acid

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

A 5% solution of Soda Phosphide is heated to boiling with excess of Urni Acid, filter hot on cooling the filtrate sets into a jelly. This jelly possesses the characteristic reaction of Diaminurate, i.e., it is readily decomposed by water with a copious emission of Urni Acid crystals. When the passage of the water into this gelatinous form is observed taking place under the microscope, it appears sometimes as amorphous matter and sometimes as "beautiful soft translucent spherules". According to Robert, the urinary secretions of Birds and Reptiles may be first voided in this soft translucent condition, and gradually gain their indurated structure, as they pass through the lower urinary passages. There would certainly be an advantage to the delicate exit tubules of the kidney that the secretion should assume this soft
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 Dihydrurate, and that in animals which eliminate their nitrogen as Uric Acid like birds and reptiles, 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 Dihydrurate. From these considerations, it may be inferred that in the normal state, Uric Acid is primarily taken up in the system as a Dihydrurate, but that it circulates in the blood as a Dihydrurate.

In perfect health the elimination of the Dihydrurate 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 ureters, into the circulation and the uric acid and urates mainly in the blood and accumulates therein. The detained uric acid circulating in a medium which is rich in sodium carbonate, gradually takes up an additional atom of base and is thereby transformed into Diurate. This transformation alters the physiological problem. The uric acid or rather a portion of it circulates no longer as the more soluble and presumably more readily soluble uric acid but as Diurate 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 Diurate 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 amolytrate, a crystalline condition and then precipitation of it becomes imminent or actually takes place." (Roberts p. 94)

We next proceed to inquire what are the conditions which hasten or delay the processes which culminate in the precipitation of forms Diurate.

If the processes which we have seen
Going on in the experiments above detailed. with regard to the solution and precipitation of sodium bicarbonate, and uric acid, in blood, serum and synovia, and the standard solvent. represent just with any degree of truth. The processes which go on in the body, and culminate in the precipitation of uric acid. I would further be of much interest to know what are the causes, which determine precipitation of bicarbonate in the tissues.

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

1) Uric acid comes into solution as monohydrate, and is converted into the hydrated bicarbonate.
2) The hydrated bicarbonate is changed into the anhydrous. Bicarbonate.
3) The anhydrous is changed, into the crystalline form.

For the sake of brevity, Roberts sums up these processes under the name Maturation.

He next inquires what effects on this process were produced by temperature. For instance, if uric acid in solution, and the addition of various saline and other substances, to the medium.

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

No factor exercised more influence in the rate of maturation and the abundance of the precipitate than this factor as will be seen from the following table. (5047).

<table>
<thead>
<tr>
<th>Quantity of Urine Acid</th>
<th>Time of precipitation of Urine Bicarbonate</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 in 1000</td>
<td>Precipitation began in 6 hours, 2 portions in 14 hours.</td>
</tr>
<tr>
<td>1 in 2000</td>
<td>Precipitation began in 23 hrs, 3 portions in 3 days.</td>
</tr>
<tr>
<td>1 in 3000</td>
<td>Slight precipitate began in 3 days; more portions in 12 days.</td>
</tr>
<tr>
<td>1 in 5000</td>
<td>A few needles of Bicarbonate on 13 days; more portions in 12 days.</td>
</tr>
<tr>
<td>1 in 6000</td>
<td>A few short needles on 13 day. In 30 days needle more numerous.</td>
</tr>
<tr>
<td>1 in 8000</td>
<td>No needles, discoverable in 14 days. A few detected in 40 days.</td>
</tr>
<tr>
<td>1 in 8000</td>
<td>No needles could be detected after the lapse of 40 days.</td>
</tr>
</tbody>
</table>

The inflammatory joint attacks in guinea pigs produced by the deposition in the cartilages of the joints of the fibrinous tisues around joints of such needles and clots. Such deposition can only take place when the fluids bathing these structures are impregnated with Urine Acid in the proportion of 1 in 2500. At the proportion of 1 in 5000, the deposited needles were about 1/10th of a Red Blood Corpuscle in 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 clotting, and even as has been already noted, might constitute free, around which clotting might take place and thus account for the thrombosis often associated with clotting. That such conditions are possible may be learned from cases of recent observations, for he obtained by quantitative analysis from the blood serum of one of his patients, thiocyanate in the proportion of 1 in 57,000.

Influence of Salts on Thrombin:

This was investigated by adding small quantities of various salts to serum impregnated with thiocyanate 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-thionate were revealed by the microscope.
2. When precipitation became more copious, and was recognized by the naked eye.

Soda Salts: He found that in serum rich in soda salts,

Bi-thionate 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.

He found that a solution of one part of thiocyanate Acid in 1000 of Serum, deposited microscopic crystals at the end of 1 hour, and a copious precipitation in 6 hours.
and that the less the percentage of sodium salts.

in the serum, the precipitation was proportionately postponed.

(a) Potassium Sulfate. All salts of Potash irrespective

of their acid radicals, retard precipitation of crystals

of Bi-urate. Potassium Iodide and Bromide, acet 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.

(b) Calcium and Magnesium Sulfate or Lime and Magnesia

show no decided action, although they appear

to slightly delay precipitation.

(c) aluminium salts and Phosphates, in the proportion of 1 to 2

per cent., does not really affect the rapidity and

degree of precipitation.

Place of Uratic Precipitation

crystals of Bi-urate cannot be precipitated in all the tissues

of the body indiscriminately. They seem to have an elective

affinity for tissues belonging to... 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 enjoying complete immunity

from uratic deposits, viz. Muscle, Brain, Liver, Spleen, Erys.
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 uric acid; 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 Tamadice.

It is worthy of notice in this connection, that
in the poisoning of Tamadice certain tissues exercise
a selective action upon the bile pigment, and by fixing
it in their substance, to protect other and more
violent tissues. Barlow, in his "Auto-intoxication"
p. 299, says: "I have shown that there are two poisons
in the bile, the biliary cells which have always been
recognized as poisons, and a substance which up
to the present has not been appreciated from a toxic
point of view, viz. the coloring matter. This is
I think a new revelation in pathology. I wish also
to call attention to the fact, that although in Tamadice
a considerable quantity of poison enters into the system
nevertheless, in the majority of cases, the introduction of
 poison is not followed by death in the organism.
n doubt protected. In the first case the Kidneys cury off part of the pigment, and the biliary acids and their derivatives. Therefore the urine becomes poisonous, the fibres of the connective tissue live. The most important of the poisons of the bile is the caluminous matter. The tissues by becoming colored withdraw from the circulation in increasing proportion. This poison and exercise gradually a condensing power. The white fibres of the connective tissue by joining the caluminous protect the Nerve cells. Thus the tissue serve to protect the organism against certain poisons. Experience shows us that the most intimate form of Taradice, viz. Black Taradice, does not chill. Precisely because the caluminous matter which is ten times more poisonous than the biliary cells becomes fixed (p. 229)."

The reason why the tissues exercise this selective action is because of their chemical composition. The tissues rich in Bada being earlier attacked than those which contain less Bada. There is the greatest tendency to precipitation when the following two factors are predominant: viz. high percentage of Taradice in solution and tissues rich in Bada cells.

Roberts gives the following table of the proportion of caluminous cells in the various tissues (p. 226).
Table: Showing the percentage of Sodium Salts in the several fluids, tissues, and organs of the body.

<table>
<thead>
<tr>
<th></th>
<th>Percentage</th>
<th></th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood Serum</td>
<td>70%</td>
<td>Blood Corpuscles</td>
<td>20%</td>
</tr>
<tr>
<td>Lymph</td>
<td>70%</td>
<td>Brain</td>
<td>20%</td>
</tr>
<tr>
<td>Synovia</td>
<td>80%</td>
<td>Muscle</td>
<td>08%</td>
</tr>
<tr>
<td>Cartilage</td>
<td>90%</td>
<td>Spleen</td>
<td>04%</td>
</tr>
<tr>
<td>Fibrous tissue</td>
<td>70%</td>
<td>Liver</td>
<td>02%</td>
</tr>
</tbody>
</table>

He says, "From the above Table it can be seen that Brain has only one fourth the percentage 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 Bicarbonate, than Cartilage and fibrous tissue, and therefore respectively 4 and 10 times more power, of resisting its precipitation in that substance" (p. 4).

And just as in the case quoted above from Rammard, fibrous tissues protect the more vital tissues. Cartilage and fibrous tissues by their "protectiveness" to induce uratic precipitation protect the more vital organs. Gravy 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
ultimately concerned in the development of rusty phenomena.

It contains more salts of soda than its congeners.

Bile and lymph. In many cases it has been
found heavily laden with crystals of Sodium Biurate.

It is usually formed in an enclosed sac or cavity
in which it has little opportunity for movement or
renovation. Blood and lymph being more
continuously and more resolutely in motion, cannot
deposit many crystals. In every situation, but when
Synovia is saturated with this Acid, it can not
itself of the excess, by depositing Biurate 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
leaves 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 employed the metatarsal bone of a pig
in aqueous sperm concentrated solution of
Sodium Biurate, and after adding a few drops
yellow form to keep the solution arctic; left it standing at the ordinary room temperature. As soon as the solution cooled, the Pith tubes practically 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 Cart, were chiefly found on the surface of the cartilage and became less frequent toward the deeper parts.

Wound of these glands we: therefore, the question why certain joints are more apt to have deposits in them than others. And also, the anomalous appearances of cartilage as an ordinary chronic or acute deposit, such as Carneus 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

As a poison (1). There is no proof that this is so. Unless Hering's 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 Burchard (Auto-intoxication pp. 51, 52, 118) prove that intravenous injections of Uric Acid in much larger percentage than ever it is found in the human body not only do not fail but do not even seem to be toxic.

He says (p51): "The enemy man can have hundreds of grammes of Uric in his deposits without having intoxicated by it. Besides I have been able to inject experimentally into the blood 50 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 (but will 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 cultivate a quantity of water which itself is toxic.
By analogy, this acid is not poisonous because its physiological homologue, urea, is not poisonous. Each forms in its separate domain. The final term of nitrogenous metabolism. It has been shown by Baer and also his Thie acid (surox). He says [561] "There are few lactic in the organism so seldom seen as much: true except albumen and the water which naturally exists in the blood." and again [267]: we are thus led to this unexpected conclusion that the substance Thie which has been for such a long time the scourge of physicians is especially injurious when it is deficient."

3. In a matter of fact the phlegm in the tissues of a gouty patient are changed to thurianis'te point with Pithole immediately before an outbreak. For, of course, no precipitation can take place yet not only are there no true phenomena experienced. But as I have shown the patient has an unusual sense of well being. So much so that those who have had many attacks have come to regard this time of phlegm the as the warning precursor of an attack.

Mechanical "The manifestations of 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 vivo 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 cells. If anything similar takes place, as an actual precipitation of microscopic crystals of 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 gastric phenomena are explainable simply as an irritation mechanically produced, or we may imagine the urate crystals falling "in sudden and copious showers" causing sharp inflammatory reaction, a regular arthritis, and seizures. Or again they may fall in quite sprinklings sufficient to cause irritation, or they may simply act as a foreign body obstructing the lymph channels, and giving rise to thrombosis.
Lucius Roberts thinks that 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 joint". He suggests that such precipitations would be very difficult to find "when the stress of saturation of the fluids with urates was released and the blood again recovered its power of dissolving these compounds. These slight deposits would be readily removed by re-solution and not a trace of them be found at an autopsy."

But such precipitations of urate, have been found and recorded many times. Lenzoni says (Rec. P. 22) "Watson, Galindo and Dufour report the finding of urate deposit upon the meninges." Comrie found microscopic crystals of urate in cerebro spinal fluid. Albert has been urate concretions in the spinal meninges. Illinois found at the autopsy of a gouty subject, who had been troubled with "feeling of constriction in the throat, chest and abdomen, as well as constricting tend in the extremities, deposits of urate, on the spinal dura mater, from the 5th cervical vertebra. The sacrum extending for some distance
along, and compressing the roots of the spinal nerves.

Andler Schroeder Von der Halle. (Le Cerveau
français Chirurgie Paris 1891 Tome 7 p 492) has seen
aggregations of Dr. Urnie Crystals in the Neurolemmas
of peripheral nerves.

Indeed there is quite a plethora of evidence of
urine deposits in various organs and tissues of the
body. Found observed here in the myocardium.

(See p 152) Inchoe in the right vocal Cord. (Archiv Vol 244)

Weiner in the caro-myocardial ligaments and joints.

Weiner in arch 62 post quoted by Buckland.

He noted that described Dr. Caufmane, Urnie Deposits and Buckland noted to same already observed
by Mr. Moore (British Medical Jnl 1863). Indeed if
needed the hugo found be filled with evidence from
complaining observers. Of Urnie Deposits in the joints,
bones, cartilage, heart and its valves, pericardial
effusions (Carrod). Kidney, meninges, muscle, nerves,
pharynx, veins, villi (Chayes, quoted by Brown p 1857).

There can be no doubt 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 supernaturated at 1 mi 6000. and that such
precipitation of urine has actually been found.
by Dr. E. G. Engle. in the serum of a healthy man. Roberts, while admitting that this explanation rests on no direct basis than that of a "strong basis of prior probability," thus sums up his views (loc. cit. p. 15). Thus Acid and its compounds are deleterious simply because of their sparing solubility in the bodily fluids. It may be said that the cause of this Acid gravel is the sparing solubility of free this Acid in the urine, and in like manner it may be said that the final cause of gall stone precipitation is the sparing solubility of cholesterol, bile salts in blood serum, lymph and synovia.

Indications for treatment as suggested by the present inquiry.

Leaving aside such treatment as is suggested by clinical experience, in order that treatment of any alteration 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 organ whose derangement 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.
have been studying.

According to these views, Urine Acid originates from the breakdown of the nuclei of cellular tissue whether by 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 Urine Acid can be excreted, but whenever by plus formation or introduction, or minus excretion, the Urine Acid accumulates in the blood and is precipitated as crystalline Bi-urate in the tissues. All these phenomena which we summarise under the name Urine Acids.

Our treatment will therefore be guided by first our knowledge of the origin of Urine Acid, and second the chemical processes involved in the precipitation of Urine Acids, 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 (p. 58), by which he thinks Urine Acids in the mammals unlike should be regarded as a "thimble" of some ancestral form which eliminated to nitrogene as Urine Acids. Thimble means urate is the physiological homologue of the entire renal activity. fluids and secretions in which the renal function
is reduced to an in primitive simplicity. In these creatures the kidneys perform one single and simple physiological act—namely, the elimination of urates, as urea, etc. In regard to the primary function of the kidneys, Nature solved the problem easily by substituting urea for urea. But why was not the problem solved completely? Why was there left in mammalian urine this crude and apparently purposeless, but to man, very mischievous residuum of urea? 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 (a) Prophylaxis and (b) Medicine.

Prophylaxis.

(a) Heredity.

This fact is more surely established in connection with an inquiry into the influence of heredity. and

though we cannot altogether assume heredity, yet the knowledge that a patient is descended from a 'urea acid stock' makes us to make use of preventative and prophylactic measures.

Dict. Remembrance our conception of the origin of the
Precaut material. The most obvious precaution we can take is to lessen its introduction. Therefore we consider what changes we should make in a patient's diet. As 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 proteinaceous articles of diet. Recent researches recommend a reduction of the nitrogenous elements of food. He says (p. 172): "The chief point of therapeutic interest that has clearly been made out, is this—that the ingestion of large quantities of protein matter is attended with an increased production of Uric Acid and vice versa. It does not appear clear that protein substances derived from the animal kingdom differ in this respect from those derived from the vegetable kingdom." He suggests an unlimited supply of fruit, starch, and sugar because experiments demonstrate there have not the least effect on the production of Uric Acid and because their large consumption enables us to restrict the intake of proteinaceous food and hence the formation of Uric Acid.

In patients with a hereditary tendency to Uric Acid diathesis, as long as the kidneys retain their normal function and are capable of excreting all the Uric Acid formed, it is, however,
not seem to be much cause for interfering with their diet. Suppose the same patient fed on the usual mixed diet of ordinary life, shows no abnormality in the excretion of this acid for 3 or 4 days, on that diet, this 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 Kabaciewski, and even of vegetarian diet, that highly nutritive nature; when we remember the experiments of Beilstein and Schultz, who showed (Levin p. 29) that the excretion of urea and amonitania 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 (Levin, p. 88) in the pronounced form of pronic. 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 baptes should be avoided, for indulgence in very large quantities of food, are so severe a trial to the kidneys, as to the stomach and liver, and besides as such functions there is always a temptation to consume larger quantities of alcoholic drinks.
than usual. In the proportions usually partaken of alcohol, alcohol seemed to exercise no effect on uratic precipitation in the experiments of Roberts, while when one remembers the experiments of Chittenden and the experiments of Levinson upon himself (op. cit. 1860), one is inclined to mention of a medical man he knew who always produced 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 urine and to continue it diminishes the excretory powers of the kidney in the long run.

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, piperaquine, sulphate of magnesia, and alkalies. There 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 one of the gouty state, and that there exists a so-called acid-diapheresis 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 Pumpt, Freudenberg (Zurich 1872) and Pontner made numerous examinations of the blood of healthy subjects and found the serum was invariably alkaline, never acid or even neutral.

It contains its high powers of self-adjustment to maintain its alkalinity. Diminished alkalinity is only found in Pyrexia Diabetic Carcinoma &c. which have no relation to this acid and alkali.

The salts of soda have been most frequently used to check this supersaturation acidity. But the evidence we have heard forward shows how vain that proceeding is. Redten has shown that an excess of soda salts always hastens the precipitation of the titre in the blood serum. "It has been shown that the addition of an alkaline carbonate to blood-serum impregnated with this acid produces no appreciable effect on the process of maturation and the advent of precipitation of the crystalline body in the medium. Hence all medication of an acute attack of soda by carbonates must be set aside. Clinical experience corroborates this.
Physicians have placed it on record that the bicarbonate of soda or the bicarbonate of ammonia have 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 lithiasis. Pyrexiae Lydiana. No doubt the urates 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 129), "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. while one of the factors of the experiment is life and living tissue.

Potassium salts drawn from Roberts' experiments to act more favourably than the corresponding sodium salts in reducing urate precipitation. Bouchardt recommends their use. (Melodeus sur alimentation de la Nutrition 1889) and Dupuy speaks favourably of their use.

Mineral springs especially those whose waters contain a
Considerable quantity of soda baths have ever been highly recommended in Gian. 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 Gian (quite in accordance with Roberts's 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-soda floating about in his blood and tissues have been precipitated into the structures surrounding his joints. The waters 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. Such springs do good at all. It must be indirectly, by acting on the liver and intestinal tract. Other springs, such as those containing sulphuric sulphate of lime, and only traces of soda may benefit a guilty 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. In fact, water-drinking athome other things being equal, would do as much good, he considers, as Roberts remarks. The other things never are equal.
The change of scene, food, abundant and close exercise, cessation from human worries or from the ennui of painless existence are some of the other things which make the difference.

According to the experiments of Pfeuffer, sulphuric acid given as sulphate of soda united with the Uric Acid, to form sulphuric acid which is very soluble and hence easily excreted. These are many other points about the treatment of Uroliths, which are of course not touched on here, as they are considered upon which the present inquiry 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 microscopically crystals, free and in course of time in which the crystals are cemented together by an albuminous substance. As Roberts says: "in gravel the uric occurs on that side of the bladder, and the Uric acid appears in the urine, and in the free state, and deposition takes place in what is strictly speaking the outside of the economy, that is to say, on the surface for crumbling of the internal integument... Naturally the question arrises. How is it that
in the case of Giant, the urine acid is deposited in the tissues while in gravel, the deposition is in the Urine.

What are the factors which come into the one case and into the other, gravel.

Deposit. The most evident difference between the two is that - in Giant, 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 secretion, where life no longer prevails, there but where chemistry alone rules, and where hitherto our methods of research become more hopefulness. We need quite waiting.

Heredity. Again we notice that in both conditions, not only to have a hereditary tendency, the manifestations of the disease, but the two conditions alternate. It has often been observed that one generation which suffers from Giant may be followed by one which suffers from Gravel. This even 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 some weeks ago.
A child suffering from Lithium. The patient
was small, restless, intelligent. Child of 8. Corresponded
almost in every detail to Sutherland's description of
such children (B.M. Journal 1872 p. 835). Such children
are usually precocious with small restless bodies.
Very changeable and nervous. Sometimes extremely
dulc. Sometimes very depressed. They fail 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 pneumonia.
It
\[\text{Such was the child we saw and to quotes from the}
\text{torture his father. A strong well-built man of 45 +}
\text{standing beside him with his hand wrapped in}
\text{bandages suffering from a sharp attack of chorea.}
\text{In all probability the child will grow to be one}
\text{of those who have a tendency to� upwards in their youth.}
\text{Not that tendency ends but becomes latent in middle}
\text{and old age.}
\]

Acid The quantity of urine acid formed gradually
decreases from infancy to old age. In a child of 3 or
10 years of age, the amount formed is 2.7 gr. per lb.
while in an adult, the amount is 0.09 to 0.11 gr. per lb.
per day. As the formation is greatest possibly connected
in infancy on account of the more active metabolism.
At that period of life there is a greater tendency to precipitation in the kidney at an early age as much so that even such authorities as Trendle have come to look upon such concretions as physiological. Lonsier (1) quotes Latham's figures of 266 newborn or very young children examined post mortem. Uric acid deposits were found in 116 cases and none in 166, and Leblanc gives a similar account of 140 autopsies in which only 28.28% had deposits were found.

Well authenticated cases are also found mentioned of uric acid inclusions being found in fetuses which died before or during birth. Such cases go far to prove that uric acid is not the result of plus or minus ossification processes as at any rate but restriction is not necessary for its formation. In fact there is a large abundance of evidence which must of space does not permit me to quote. All tending to show that in the early years of life uric acid 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 washed out by the urine.
opinion appears to be shared by Hesseh, Lutherau.
and de Costa. That the blood and urine should contain
a large proportion of urea 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 hemoglobin absorbed 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 periodicical or occasional passage 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 existence which
remains with them all their life.

Inherent tendency of the urine to the spontaneous liberation
and precipitation of this acid.

We have already seen that there are various forms of this
acid salts: (1) the neutral urates which cannot exist
in the human body. (2) the urates which exist and
are known only as pathological excrescences or tophi
in the neighborhood of gouty joints. and (3) the
mandurates which come into existence whenever
this acid is brought into contact with any of the body
fluids blood, serum, lymph, synovia. Indeed.
This order of facts seems to be the only physiological form in which Uric Acid can exist in the healthy body. It is where 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 mucinate and passes through the Renal epithelium as mucinate. It combines with the alkaline bases of Bicarbonate and Ammonium. In a state of health, these combinations are not disturbed, and the Uric Acid is thus slowly and uniformly excreted. But under certain conditions these normal combinations are interfered with, and the Uric Acid is set free in the kidneys. Unless 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 aseptic change, taking place (by adding a few drops of chloric formic), 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 liquor, 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. Then Urine 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 Urine Acid in Urine.

Urine Acid occurs in all urines even in the clear and non-sedimentary as Quadrinurate. To 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 Quadrinurate. It is amorphous and decomposed by water with a free emission of Urine Acid crystals. It might be objected that this is not Quadrinurate but B. Urine. But we have shown B. Urine cannot exist as such in urine. It is instantly changed into Quadrinurate.

"Therefore we may conclude (Roberts' Op. cit. 184) without any misgiving that the Quadrinurate is the form and the only form at which Urine Acid exists in normal urine... and may draw the inference that
When Uric Acid makes its appearance there in any other guise that went is due to secondary changes. In the Quadrivium. Now regarding the Urine.

It is simply a fluid which holds in solution there 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 Urine, but as representing a special nitrogenous metabolite. It is as has been shown the result of the oxidation of nucleic, an albuminous substance which is contained in the cell-matter and distinguished by its richness in phosphorus. The phosphorus set-free alone mites with the ever-present alkalies 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 superphosphate preponderate the urine is acid and when the di-metallic, the urine is alkaline.

We have therefore in the urine exactly the conditions under which Uric Acid is easily liberated from the Quadrivium is split up by the water into free Uric Acid and Pyro-Uric, and thus half of the Uric acid is set-free. But the Pyro-Uric set-free is in the presence
of the superphosphate, immediately by double decomposition
it transformed into Diamondate. Thus
" two atoms of Diamondate with one atom of superphosphate,
change into one atom of Diamondate and one atom of
molecule phosphate. Thus: (Poultz p 42).

Diamondate Mono-metallic phosphate Diamondate Di-metallic phosphate

\[2 \text{M} \text{H}_2\text{U} + \text{M} \text{H}_2\text{PO}_4 \rightarrow (\text{H}_2\text{U} \cdot \text{M} \text{H}_2\text{U}) + (\text{M}_2 \text{H}_2\text{PO}_4)\]

These alternating reactions breaking up of Diamondate.
by water into Diamondate and free Thio Acid and decomposition
of Diamondate, by double decomposition of Diamondate.
with mono-metallic phosphate go on progressively till
all the Thio Acid is set free.
The 1st Step is confirmed by experiments already made
by acting on Diamondate with water.
The 2nd Step the transformation of Diamondate in presence
of superphosphate into Diamondate is verified by
the following experiments.

A saturated solution of calcium Diamondate
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 known
down which upon examination is found to possess
the characteristic reactions of the Diamondate.

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 Diammoniate, 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 Diammoniate in presence of superphosphates 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 small quantity has been precipitated, but until the whole of the Uric Acid is set free.

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

There must be some inhibiting factors and if so what are they?

It was found that this inhibitory power existed partly at least in the excrement of the urine.
the chief of which are those of chloride, phosphate, sulphate, of lodinium, 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 quadrinurates.

The method of subjecting this question to the test of experiment was as follows. A drop 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, 25 minutes.

The results were: Chlorides and sulphates some inhibitory power. Potassium salts more inhibitory power than lodinium or Ammonium salts. Di-sodic phosphate about the same as lodinium chloride. None so powerful as natural healthy urine. Di-potassic phosphate gave the best results. Alkaline urines had no disintegrating effect on the amorphous deposit.

The colouring matters.

When attention was turned to the colouring
matters. It was observed that amorphous urates were always deeply stained by urinary pigment, but deeply tinted urates were broken up by water more slowly than pale urates. That the Dachshund 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 felinest 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 Urice Acid Gravel

1. Retarding influences. We have just shown that the presence of albumin was pigment caused an inhibitory effect on the precipitation of Urice Acid from urine.

2. Hashing influences. Roberts obtained the following results:
   a. Precipitation was hastened when the urine was 30% sodium.
   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 Urice Acid to urinary water.
a. 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 Robert's 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 bicarbons.
3) Low pigmentation
4) High percentage of Uric Acid.

Other causes of its formation:

1) Diet. To meet the old theory that Uric Acid resulted from the defective metabolism of the protein 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. Were the factors which caused diminished oxidation of the products of retrograde metabolism and that of oxidation of these products had gone further. True acid would not have been formed. This theory becomes inculcative not only from a consideration of these experiments. but also because all the most recent experiments show that true acid is not increased to any appreciable extent by taking a large quantity of nitrogenous food.

Where already mentioned Robert Conolly had True acid connections derived from a diet poor in the animal constituents. We have an interesting object lesson in the relationship of True Acid to Passes and Stomachs who lie side by side in India. The Passes are much older and in spite of the protecting influence of the climate (in favoumi) the Stomach is chiefly affected. It does not eat much. and on account of the iniquitous salt-taste consumes very little salt. His urine is therefore deficient in cultures and he suffers to a high degree from stone. The same thing may be seen among those badly fed children and among English agricultural labourers, who lie downly on vegetable and non-nitrogenous diet and who are subject to the various diseases of cities. among whom stone is rare.
There contains only 2 4 7o of salivary constituents.
Wheat-flour 5 1 7o, Oatmeal 2 5 7o, Milk 5 5 7o, meat and
fish 5 5 7o.

On the other hand, among sailors as a class, stone is
very rare, as their diet consists largely of salted meat.

The Chippewas quoted by LeCounte, considers this for he
was able to find only one case of stone in the history among
34,000 English sailors; while this affection is by no means
uncommon among their officers, whose manner of living
continued more to that of men on shore, it less salt provisions

Roberts therefore recommends a liberal consumption
of salt in the diet of patients troubled with stone and
drinks or stone.

Mr. Clowright of King's Lynn. (On the cause and distribution
of Calculous Disease, 1816, 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 stone, which have come under his notice,
comparing with stone cases. He says that is one fact
of Norfolk. The Marsh-lands, where the drinking water
contains too 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.
reddish-brown granules of sand. In Concretions of the above
agglutinated together, formed 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 framework. It is structureless, uniform Consistency
yields no evidence of cellular structure or nuclei, nor any
trace of organization. According to Lebedebin the Uric Acid
is deposited in the Epithelium of the tubules of the Kidneys
and such 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 Glomeres. A Dr. further informs
me that it is no uncommon occurrence to find considerable
quantities of coarse reddish-brown sand. When cutting
them the hairs of bees, bumblebees this is urine acid
sand. Sometimes these Concretions in the pelvis become
so large that they cannot pass down the urineters, but by
blocking them in whole or in part: give rise to
Hydronephrosis and other Pathological Conditions.

Pathogenesis of Stone

It is not easy to obtain every clean
Conception of how the uric acid in the urine, especially in the upper tracts of the urinary passages, gave rise in some cases to true concretions, which are avoided 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 adduced by Roberts shows that there are a number of factors acting separately or together which brought about the deposition of uric acid in the urine, such as: (1) high percentage of uric acid in proportion to the quantity of urine. (2) the reaction of the urine. (3) its richness in calcium, especially the chloride and phosphate of calcium, and (4) the quantity of pigment. Levison on the other hand examines these factors in causing the uric acid deposition.

Hereditary. So long as we do not know what peculiarity of metabolism the uric acid contains 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 his predisposing cause.
2 Aqae. The urine the younger it is contains a greater proportion of urea acid. According to Pfeiffer, urea acid appears to be produced in all ages in a gradually decreasing proportion, so that it reaches the minimum in old age. In other words, it keeps pace with the active metabolism of the body. Creatinin & uric acid are common in the young.

3 Uric aciduria. In this disease in which the production of urea acid is excessive, the normal quantity of uric acid is formed. The formation of uric acid is very common.

4 Other diseases. When associated with excessive urea acid production, one finds it common to cause deposits, e.g., in Pneumonia, in which Von Tschache always found it common to cause uric aciduria. Deposits are common. He says (p. 123):

"E自己的 opinion is that different results are obtained in the analysis of the blood in cases of the lungs, but in agreement with the repeated quotations, which I have just mentioned, fever, as well as carbonic acid, causes the urine to color one. Must we strike one. That I constantly have formed urea acid"
in all cases of Chronic Pneumonia which were investigated during the febrile stage. quite in agreement with Lulow's statements.

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 gout is chiefly a disease of the very young and that such patients often develop gout in later life. Here is something more than a presumption. that gout is the primary condition.

Lewins experiments on himself (with a pronounced and hereditary predisposition to uric acid cystal) show that the proportion of uric acid in the urine is not the only factor influencing deposition of crystals. for it may occur both with a normal or an abnormally low excretion of uric acid (Lewin, op. cit., pp. 110-111). Increased deposition was caused by very active physical exercise, and also when alcohol in the form of wine was taken. Again we may recall the case of a woman to medical friend who could induce urate precipitation in his urine by taking a very small quantity of wine.

Reaction. This is one of Robert's Canon's. Neutral and Alkali urine can hold in solution a very considerable quantity of uric acid. while from an Acid urine...
It is very readily deposed.

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-hydro 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 phosphorus, which is thus set 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, p. 548) i.e. at a time when more uric acid is formed.

The alkalinity of the blood is also diminished by very active muscular exercise (C. Hutchinson, Lancet, 25 Apr. 1896) and (Cohnstein Verh. Physiol. 606. 1852), by convulsions from strychnine, by cyanosis, Cachexia Carthonica. Pathological Conditions of the Liver and by fever, all of which conditions are characterized 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 varies 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 two parts, with relation to alkalinity: One, during the day, when food is being taken, he calls the alkaline tide, during which Urine 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 valuable to deposit crystals of Urine Acid, even when it does not contain a high percentage of that body.

A calculus found in the pelvis of the kidney has long appearance of having grown there. They have even been found branched. The branches corresponding to the calyces, and even extending up some distance into the collecting tubules. Lobstein affirms that these take their origin in the Kidney tissue, and that he has found them
in the convoluted tubules. Probably the smaller concretions are formed here, and in the loops of Henle, and are washed thence by the plas 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 epithelial but himself. Many other authorities have observed the crystals in the lumina of the tubes within the rows of epithelial cells, as if they had been formed there.

Rulots opposes Lobstein and maintains that in gravel as in stone, 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 reactions by morbid changes, proliferation, and the formation of casts. The albuminous basis becomes infiltrated with crystals. The small concretions at first formed are washed into the collecting tubules, 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. This grows by repeated additions of Thio Acid. While the Muscular Membrane of the Pelvis, supplies the albuminous substance required for cement. and thus concentric layers are formed in which the crystals are deposited.

Sir I. Changer Stewart (Albuminuric 1887-160.) admits that renal irritation and consequent Albuminuria maybe caused by the passage of Thio Acid and oxalates through the delicate tubules of the kidney.

Martin Ruge (Zeitschrift für Schmerzkrankheiten 1871) observed that in examining the urine of 147 newly born children, hyaline casts in 14 cases. and on the first day of life Albuminuria in all. and attributed this to irritation of the kidneys by Thio Acid precipitation.

Uggman, who found Thio Acid in the urine of patients suffering from temporary or physiologicalAlbuminuria thinks that the Thio Acid is the cause of the Albuminuria, and that the deposition of Thio Acid crystals on the acid albumin in combination, with temporary Albuminuria, is a first step to the formation of Thio Acid Calculi. Abundance of evidence of a similar nature, did space permit might be given. But we shall quote from Levin Niessz's Observations.
(Mediskt Med. Archiv. 1918 p. 43) "In 27 out of 50 cases mentioned Uric Acid gravel was accompanied by Albuminuria. In 22 there was a trace of Albumin.

The sediment was examined microscopically in 25 cases. 14 of which contained Casts, and Kidney epithelial cells and 3 Casts only.

In other 27 hospital cases, 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 Albumin, 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 13 Casts and epithelial cells and in 1 epithelial only. In certain cases it was established that the number of Casts was in proportion to the quantity of gravel. Twelve of the patients here referred to died, and were examined post mortem and in seven of these there were indubitable signs of advanced Kidney disease.

Lemmi 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 Convulsive 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 many times meeting casts and uric acid crystals in the urine, Lenzi tried to prove that the explanation was that the casts may really originate by the deposition of crystals in the urinary tubules. Precisely that he laid a strong hereditary tendency. If uric acid gravel only controlled by continuous use of alkalis, 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 alkalis.

Olasar (Fürhet und Wachsmuth 1821) 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 of the patient was allowed a large
Quantities of beer. He thought the casts were caused by the direct action of the alcohol; in the kidneys, this probably the cause was indirect, the alcohol causing first an increased production of uric acid which in the tubes 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 tubes 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 formation may be said of a true kidney carcinoma.

Lewin (April 22nd) has summed his conclusions:

"When the chemical composition of the urine is such that uric acid becomes deposited in the kidney, the crystals are fixed upon the lining down in the tubes of the cortex. Tubuli contorti it belongs as they are not numerous they may be washed out by the flow frome 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 epithelium, characterised by the formation of casts...
Spurious 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 chronic condition of the mucous membranes.

By means of this an albuminous substance is excreted and deposited in consecutive layers, as the concretion grows in size, from the additional deposit of uric acid. This must differ from acetate of sodium, when one remembers the method of action of the uric acid filter. Uric acid is deposited in an already diseased kidney, and plaits have already formed in the tubes. The concretions will form more rapidly; this will also be the case when pieces of necrosed tissue; foreign bodies exist in the kidney, as they hinder themselves to the infiltration of uric acid crystals.

If this pathological process continues for some time, it will not only tend to the formation of larger concretions, but may also cause chronic disease of the kidney, by extension from the epithelium to the kidney tubes. Thence this 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 easily intercept must the excretory power of the kidney and as choruses states the true acid plants to be slowly retained in that stage of the kidney affection in which the urine and other easily soluble constituents of the urine can pass off.

Here perhaps lies the explanation of the fact that symptoms of cancer in stone of the kidney very often occur in younger men who in later life are affected with typical cancer.

**Symptoms.**

The more crude and obtrusive indications of renal calcic with its abundant symptoms of nausea vomiting and radiating pains are well known and everywhere described. But these are more obscure and not always well described symptoms of the existence of true acid crystals or small concretions in the kidney which unless the physician warned by the existence of the densitons look and for may easily be passed over or attributed to a wrong cause.

In children there occur phenomena of pain in the kidney pain rigor region accompanied by churning or feverishness.
and very often accompanied by constipation which 
unless the practitioner observe also, but at the same 
time the urine is loaded with moras may easily 
be attributed to intestinal conditions or worms. 
and grave lead to measures for opening the 
bowels instead of a course of alkalis.

Haematuria. Sometimes cases of haematuria arise, which 
do not yield to haemostatic treatment, but when 
along with the haematuria is probable cause. 
True and crystals in the urine are observed and 
treated by alkalis. The haematuria ceases. In the 
same way paroxysmal albuminuria may yield 
its explanation and treatment similar symptoms 
are influenced and treated by. Sutherland (in P.M. Journal 1872, p. 855).

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 loin, or 
a copious deposit of lithrates. Its true character 
may be summed. It should be remembered 
however that children seldom complain of pain 
in the renal 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
Cancer, 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.

The most common symptoms are:

1. A dull pain over the lumbar region occupying the position of the kidneys. It is more nearly a tenderness rather than a pain and is not increased by pressure, but is aggravated by the patient lying in 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 periarteritis. Though it is differentiated from that condition by adhering to the under and anterior aspects of the thighs following the distribution of the anterior and sciatic nerves.

3. Anaemia
4. Constipation
5. Privy
6. Periodic states of depression, without hallucinations, with tiredness, shortness of breath, almost always accompanies the repeated temporal sensations characteristic of cancer formation.
opinion. These symptoms correspond with those characteristic of gout. Migraine similar symptoms may be caused by deposition of crystals of oxalate of uric in the kidneys.

Treatment.
There are 3 objects in view.

1. To act upon the respiratory and chemical constitution of the urine in such a way as to diminish the tendency to urate 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 diminish concentrations already formed in the kidneys.

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 Cantoni recommended a diet in which flesh predominated, Dr. G. a diet from which flesh in all forms was carefully eliminated... and Le Bothe the same diet he prescribed for obesity and gout.

The statistics which have been collected.
seem to show, that a diet too poor in alluminous substances, has a tendency to cause uric acid conditions, and in this connection we ought to remember, Roberts' demonstration of how uric acid crystals are frequently formed in the urine of poorly fed children, rice-fed Indians, and the vegetable-fed agricultural labourers of England, and especially of Scotland. and the recorded instances of uric acid abundance during prolonged fasting.

Alcohol.

...should be avoided, both because it increases production of uric acid and also because it tends to produce dilation by irritating the kidney tissue, by the precipitated uric acid crystals.

Much drinking of water or tending to make the urine, very dilute should be avoided, because... permanent decomposition more rapidly in pure water than in urine. At the same time so 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. it 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.

...a considerable quantity should be taken daily as it has been shown experimentally (Roberts) to hold...
True Acid in solution. "The richer it is in solutions, 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, it is not always explained 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 tubes, 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 water of Lithia can be shown to be very soluble in water. Clinically however, and in practice, Lithia has been pronounced insufficient by many competent observers. Roberts (p. 120) says: "If these baths (Lithia Piperazine) have any beneficial action at all it is certainly not due as has been supposed, to their salutary action on the material of the stones, but rather to the effect in the formation of the latter substance."

"When however Piperazine is dissolved in water the solution has little or any action upon Uric Acid and experiments have likewise proved the drug has no influence upon the formation of the latter substance. This..."
a strong testimony after using it in 30-40 cases.

Indeed. Lelloue has been shown to diminish the
secretion of urine acid. It has been painted and in the
Lancet for 1825, 184. By" (Revis' Chemical Analysis, 18;
Lelloue given by the mouth was no one as a solvent
of urine acid. Because it forms a nearly insoluble triple
phosphate with phosphate of lime or with the triple phosphate
of ammonia and soda. Subsequently present in animal fluids.

Hence, Chemistry and clinical experience agree on
this point. and give us another warning against jumping
hastyly 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
missing "life". The process which changes the
condition of the experiment materially.

We must learn however, to recognize the "life" of
the" and "something like body, to the Real Med. Association
in the study of experiments with Pilocarpine and Syringine
(MM's, March 1996, 1991). The conclusion he came to was,

"Pilocarpine Syringine when added to a urine tended

to deposit urine acid quickly, are capable of hindering
the deposit during standing. Syringine is a more
potent solvent for urine acid than Pilocarpine.

Both Pilocarpine and Syringine when taken internally
appear to increase the elimination of urea 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 solubility power, the prolonged administration of these drugs in the end causes a diminution in the quantity of urea acid eliminated by the kidneys.

Piperezin and lysergic acid are both cholinetics and cause an increased elimination of nitrogen which is partly due to the increase of the nitrogen in the urine acid and in part due to its cholinetic action.

Prof. Kühn, in a lecture reported in the "Deutsche Klinische Wochenschrift" 19 Aug. 1876, p. 352, says:

"In weiterhin haben wir zahlreichs festgestellt, was auf die Acidität des Harns diejenigen Mittel einwirken welche in dem Pute stehen besonders als Lösungsmittel der Harnsäure zu dienen. Wir untersuchten zuerst den effect der organischen Basen Piperezin, lysergic usw. welche in Reagensglas, so grosse Mengen, Harnsäure zu lösen vermögen und welche nach den Angaben vieler Autoren auch dem Urin ein grosses Harnsäure-loösmungs-ermöglich verleihen.

Unsere Versuche zeigen dass die Organischen Basen in der That untersetzt in dem Urin übergingen und nicht etwa unter NIH-Abspaltung "ersetzt"
Ursprünglich wird durch die Aminduren die Acidität der Urin vermindert. Wie aus folgenden von Benedikt ermittelten Tabellen hervorgeht (ver. = 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 Urin Acid. We investigated first the organic bases: Piperazine, Lysine, Anhydro Lysine, which in the test-tube are able to dissolve so that a quantity of Urin Acid, and which according to the statements of many authors also lead to the urine a means of dissolving Urin Acid. Our investigations showed that the organic bases, in reality pass over into the urine, unchanged, and do not change (bleiben unverändert).

At all with Ammoniac production, as is seen from the following table, etc.

He then asks, whether these bodies go into the urine together with the regeneration of diet, and especially of alkali bases. But these still other means which in a specific manner, unter Anwendung Urin Acid, und des Ammoniak. (-1825) - Dies dies. nicht die, ohne genannten organischen Basen, noch auch das Lichion verringern, branche sich nicht nochmals. aneinander ansetzen. Diese Mittel gehen in den Urin, und verengen sich mit den vorhandenen.
Menger herein: so dass 2/3. des größten Theil. de
m in Genommenen Lithions als Chlorolithium und
wur ein kleiner Rest. als, humanes Lithium
mit dem obigen vorgang =. That the above named
organic bases. zur even Lithium are able to do this
I do not require to explain more. The base in
pass over into the urine. and unite with the existing
acids. according to the pre-existent quantities of those
so that, for example, the greatest part of the Lithium
which has been taken appears as a Chloride of
Lithium, and only a small remainder is able to
appear as, Acetate of Lithium. (I must not give any
more of the text but simply the translation).

There is one body which can dissolve that
Acid, independent of the Laws of the operation of
Muriatic and quicksilver. But it is a substance what
made operation (dissolving), has been known for years.
and which yet is only little employed. Because
there has never been any Commercial demand for it. Urea.

Last year ago, Rüdell established in the pharmacological
institute at Heidelberg, that there is able to dissolve
Urea Acid. He brought forward his circumstance
in order to show why a normal urine. so much
more Urea Acid can be dissolved than is possible
in water. Thereupon Mering recommended that
Thatie patients should be allowed to eat much meat for he who eats much meat has much trouble in his innir. But I believe he who allows his patients for this reason to eat much meat warns him with the one hand in order to heal him with the other. It is better that one should avoid abundant urine acid formation through eating much meat and give to his patients urine ready made (fertiges Präparat).

In this way has Rostfeldt in Berlin employed at some last year, and in this way (as I have shown in the report at the last Congress für Innere Medizin) it has been lately employed by many Clinicians.

I myself have favored for almost 2 years in a great measure the therapeutic use of pure urine. I believe I may venture to say that this material offers an excellent means against the urine Acid diseases.

I gave it to such patients as have passed urine Acid concretions and who once more suffer from Calcul (renal) or rather Harnstau. I do not judge once more to point to the well-known fact that an abundant supply of alkaline fluids in many cases under suitable circumstances can deliver the patients from the symptoms without threat, but any doctor will willingly possess a means, which can alone perform the same service as the
new established method. (die bisher empfohlenen Methoden)

Iprescrib.

UNNEE PUNICE. 10.0 L - 20

Aq. pura destill. 200.0.

Seemlich fort.

There are no seen harmful Consequences from this Medicament. Although I several times have prescribed up to 500 grms. Consequentially. It much derived Consequence is the often remarkable increase in diarrhoea upon which I have made remarks in another place.

The above fact was also established by Bauchard, who refers to it in many places, in his Autohaemorrhagia. On p60 he says, while recapitulating the toxic principles which he demonstrated in haemorrhagia. "We find there are seven of them, there is first a diuretic substance fried. Fungoee nature: since it is destroyed by heat. It is not fried 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 character. The property which experiment allows us to attribute to them. that of Augmenting the quantity of urine. We have thus the right.
is easy, that this diuretic substance contained in normal urine, is no other than urea. Thus in this way, although it is a product of dis-association, plays a useful role in the economy. It possesses the property of forming 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 three causes also influenced secretion of urine acid in Klemperer's experiments.

The other points insisted on by Klemperer are: There must be sufficient diuresis. The gram of urine acid requires 1 liter of water for its solution at body temperature; the patient must therefore drink a sufficient quantity of water.

In much sweating and exercise should be avoided. The treatment of Jewish diabetes in this respect from Cavent.
(c) The quantity of urea acid in the urine should be diminished. For urea acid must not be regarded (as has been shown already) as representing a stage in the production of urea but as representing a special nitrogenuous metabolism. Care should be had not the limit of food taken. Urea acid excretion on a milk diet is scarcely any greater
There is no general quantitative relation between the mucin in the food and the Uric Acid in the Urine (Erkanszki). For mucin may also be excreted as Urea, just as Uric Acid may be, when taken by the mouth (opposed to Hais'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. The ingestion of certain bodies leads, just as the taking of mucin does, to an increase of Uric Acid in the urine; therefore excess of Tea, Coffee, and meat extracts should be avoided. (Confirmed by Hais).

2). The acidity of the Urine should be kept below a certain level, to prevent the precipitation of Uric acid. He therefore recommends Lod. Caviar or Pot Citrate 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 fact is common...
to these two conditions as Urine Acid. And are inclined rather to look upon the Arthritis 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.

Arthritis (defined originally by Pidans, and accepted later by Chantler and Hutchinson) is a diathetic habit of body from which arise as branches two main and distinct classes of disorder, commonly recognized as Chure and Rheumatism.

In the most recently published work of an authority on Rheumatism (Rheumatism & Medicine 1873), not a word is said about Urine Acid as a cause in Rheumatism, but Lactic Acid is shown to be the offending material. "A product of meat assimilation or imperfect time metabolism" (p. 23). On p. 35, he says: "Increased formation of Lactic Acid is one of the essential features of Acute Rheumatism. And no theory of that disease can be regarded as satisfactory which does not recognize and account for this increase. Thus the lactic acid theory fails to do." And again in p. 59 et seq. "The fact which has been demonstrated by Aron and others, over and over again, that urinary Acid does not exist in excess in the blood in Acute Rheumatism." Where Lactic Acid is
The cause of disease in a patient of paralytic weakness is known as arthritic rheumatism. But while the arthritis is not the outstanding feature, muscular rheumatism is the result.

Besides the pathological afflatus of rheumatism are malaria (malarian) chorea, and by them are cold and gravel.

On the other hand, this acid manifests itself in cold and cantiness. These two states may never pass into the other, but more commonly cantiness includes hurried cold and cold once declared, passes sooner or later into cantiness. Their etiology is the same, and we have no choice left but to regard that which they possess in common as the essential point in them, and that which is not common in their manifestation as the non-essential point. So also with cold and rheumatism, the common factor is the arthritic sickness. Viewed from this point also, it is easy to conceive why the same patient may be afflicted at one time with cold and at another with rheumatism.

Highly we value the opinions of Dr. Goodhart, we cannot agree with him nor find support for his statement in his paper (BM Journal 1891, 252).
that "in summing up what has been, we must say that under some circumstances, a certain period of life. Claud is Acute Rheumatism." We feel bound to say his evidence does not justify that conclusion.

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

Were renal disease, in itself, capable of bringing about the urine acid disturbance but Claud, as it appears, should develop Claud sooner or later. This is far from being the case.

There is much too that we don't know about the matrix deposits. E.g., we do not know whether the matrix deposits are incorporated 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 Reuben (excite), 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 to another direction: for example, the rapid disappearance of the inflammation from the joint toe under the influence of cold affusion of calcemic. (The peculiar benefit of calcemic is not seen in any other inflammation, due to Puckett and cite p. 215). In other words, it is not easily explained by the assumption that its cause is the mechanical imitation of the Di-Urte.

Summary.

We have endeavored to show in the preceding pages that: Urine acid is formed in the body by the disintegration of the albuminous substances of the tissues especially of the mucous (Horbuziowski).

2. That its excretion becomes increased or diminished by all factors (diabetes, drugs, poisons) which bring about a more rapid or slower disintegration of tissue (Horbuziowski).

3. That in every individual the excretion of Urine acid remains nearly constant after the 12th hour of fasting, but that after a meal, the excretion of Urine acid rises rapidly and does not rise again for several hours; that an increased excretion of Urine
takes place later, reaching its maximum 9 hours after a meal, and then falls again. As a consequence we infer that uric acid is derived from the albumen of the food, and uric acid from the tissues of the body. (Walker).

That the taking of food, especially flesh food, causes a temporary (digestive) leucocytosis, which arises from the nucleus of the ingested food, or from the increased cellular activity during digestion, is a fact which accompanies digestion.

The cause of the increased excretion of uric acid after meals. (Horbayowski).

The fact that uric acid excretion is greatest in infancy and least as age advances. ni fact keeps pace with metabolic activity. Favors the same theory.

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 Ruege and Pfeiffer), and after ingestion of meals (Horbayowski), or pathological as in leucocythaemia (Lauche, Benedict, Stadthagen and others), in Pneumonia, Cancer and cutaneous Burns. and after the exhibition of Thiorcarpine (Horbayowski), after Alcohol (Chittenden), Camper, and Seirion), and after unusual physical
That urinary acid production is not dependent on destruction of leukocytes alone, but also on the disintegrative and metabolic changes in the totality of the organism; changes which are influenced by alimentation (Levriére), but not in the proportion of the nitrogenous ingested, while the production of acid is strictly proportional to the latter.

That whenever elimination is interfered with, as in the kidney disease, urinary acid accumulates in the blood.

That the normal or physiological form in which it exists in the blood, or is excreted in the urine is that of a Quadrinurate: glosidium Phosphinium Calcium Magnesium ++ (René Tous, disturbed).

That the pathological form in which it is found in the body, is that of a Bi-Urate in Early Connective and Tissues.

That the Quadrinurate 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 kidney. The Bi-Urate thus produced, exists at first in the hydrated or gelatinous form,
but with lapse of time and increasing accumulation, passes into the anhydrous, or crystalline condition.

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 Bicarbonate is found deposited chiefly in fibrous tissue.

14. That it produces 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 (Burchard). That also after excretion in the urine it may under certain conditions become the cause of much injury throughout the urinary tract.

15. That all acid urine has an inherent tendency to precipitate the Uric Acid from its solution as Concentrations, as fine sand or larger Concentrations of Uric Acid. (Roberts).

16. That the conditions which tend to cause or hasten the precipitation are: (a) absence of proper ions, crystallization. (b) a high proportion of Uric Acid. (c) a high degree of acidity. (Roberts).
Other determining agencies are: (1) Leveredness of the age, (2) the younger the urine the greater the proportion of Uric Acid. (3) Leucemic fluid. (4) Other Diseases as Pneumonia (von Tappeck), etc.

5. Very active physical exercise. (6) Alcohol. (Lemire, Bichot).

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

That Uric Acid manifests its presence in different ways in different patients, according to their underlying disease, as, a虛 or Gauntiness.

That Gaunt occurs when excess of Uric Acid manifests itself in a patient by gaunt disease.

That Gauntiness occurs when Uric Acid in excess is manifested in a Patient without this underlying disease, and consists in a general change, both functional and structural - the functional change as it affects the tissues, Gauntness is abnormal acidity (i.e. lowered alkalinity), and as it affects the tissues, measured irritability and lowered resistance. It is most manifested in the nervous system by a great increase in irritability.

That Uric acid is present in least quantity in the body in the highest conditions of health. That in advanced urates commonly increase
and this is an indication of a lower level of metabolism constituting a degradation to a lower animal type (Sir W. Bruce quoted by Sir J. Duckworth op. cit. p. 87).

25. That the secreting functions of the kidney, for urea and uric acid, are separate and independent of each other.

26. That as regards treatment, while tannin独cells are all powerful to prevent precipitation of uric acid in the urine, they are of no value (as has been maintained) to cause solution of urate 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 tannin独cells in that is concerned, they are largely prescribed, especially on the Continent (as mineral (natural) waters). In spite of the experimental evidence which has derived to them any important direct solvent power for urate deposits, and placed them under suspicion of increasing their precipitation.

27. That great care should therefore be taken in adopting the testimony of experiments in vitro, especially when they are contradicted by clinical experience.
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.