The Value of Urotropine, Hexamethylenetetramine and Metramine in the prophylaxis of Scarlatinal Nephritis.

Derived from observations on 300 cases of Scarlatina.

Being a Thesis for the degree of Doctor of Medicine in the University of Edinburgh.

by

Herbert Pank Thompson.

M.B. Ch.B. Edin. 1802.

April 1906.
Introduction.

In the following pages I have put on record certain Clinical Observations more especially in relation to Nephritis in 300 cases of Scarlatina, which were treated at the Edinburgh City Hospital from the 9th. August 1905 to the 5th. January 1906.

I have had access to the City Hospital records from 1900 to 1906, and in my study of the cases and calculations therefrom, I have paid particular attention to Nephritis.

As the only method of arriving at a satisfactory prophylaxis against the Nephritis of Scarlatina is dependent on the study of the cause of the disease, I have given what I consider the most important views that have been expressed on this point.

And to appreciate the various attempts that have been made in counteracting Scarlatinal Nephritis, it is necessary to make a short review of them.

The more recent attempts have been in the way
of Urinary Antiseptics; and following on the good accounts given by 4 observers in Austria, Germany and Roumania, with regard to the prophylactic use of Urotropine in Scarlatinal Nephritis, I essayed to combat this dreaded complication by means of Hexamethylenetetramine and its two proprietary equivalents, Urotropine and Metramine.

The 300 cases, to which I shall particularly refer, were under my constant observation. In every one of these cases the diagnosis of Scarlatina was corroborated by Dr. Claude B. Ker, Medical Superintendent of the Hospital, to whom I am deeply indebted for permission to carry out my investigations.

It is true that one cannot dogmatise from the observations on 300 cases of Scarlatina, but I think that the results obtained are of interest, and I hope of some practical value.

There is no literature to the effect that these drugs have ever before been used in the British Isles for Scarlatinal Nephritis or the prophylaxis thereof.
The Causation of Scarlatinal Nephritis.

Before considering the various means that have been tried to ward off Nephritis, it would well to review shortly the various views that have been put forward as to its causation.

Early Albuminuria.

Thomas and Bartels are of the opinion that early Albuminuria, i.e., Albuminuria in the first 10 days of the illness, is distinctive from that which occurs later.

Professor Wyllie also, in his lectures on Systematic Medicine, says that a little febrile albuminuria in the first few days of the disease is merely indicative of exhaustion.

Steiner and Einschitz suppose Scarlatinal albuminuria, whether early or late, to be the result of Renal mischief of the same sort, though not of the same intensity.

x Thomas: Ziemssen's Cyclopaedia.
Warburton Begbie thought that early Albuminuria resulted from an escape of albumin from the renal tubules, in a process of desquamation of the renal Epithelium, analogous to that of the cuticle, and that late albuminuria was a symptom of inflammation of the kidney due to chilling.

But the view that Early Albuminuria is due to Pyrexia, as first described by Gerhardt, as "Febrile Albuminuria," is the one usually accepted.

Astley Gresswell regards Early Albuminuria as not due to Pyrexia qua Pyrexia, but considers that early and late are both due to the "same sort of mischief, each being as much an essential of the train of determinations in Scarlatina as the Tonsillitis, the Rash, the Cervical Adenitis or other determination."

The late Professor Sir Thomas Grainger Stewart found albuminuria present in almost a third of 505 cases. Astley Gresswell: "Natural History of Scarlatina". p. 91.

Grainger Stewart: "Brights disease."
apparently healthy male patients. A large proportion
of this was in all probability due to fatigue, as in
many cases the urine had been passed after exercise.
Dietetic idiosyncrasies, severe central nervous
system disturbances, chills and Postural Albuminuria
are further examples of Functional Albuminuria.
So that the mere presence of albumin in the urine is
not indicative of organic disease of the kidney.
On the other hand Litten (1) says even a severe
Nephritis may run its course entirely free from
clinical symptoms.
And that scattered casts without albumin have no
essential pathological significance and may occur in
healthy people.

(1) Litten: Beiträge zur Lehre von der Scarlatina.
Charité-Annalen 1880 Bd VII. S.162.
Cohnheim (1) says that the substance (whatever it may be), which involves the kidneys consequent upon Scarlatina, circulates with the blood, and with it makes its way to the kidneys.

The first badly exposed part is the Glomerulus with its epithelial covering.

The toxin may have a varying selective tendency — either the vessel walls, or the epithelium in the Glomerulus.

One must suffer as soon as the other is much injured.

It is probably something other than organic elements or micro-organisms which cause Scarlatinal Nephritis.

The Schizomycetes, which have been found in individual cases, may have become located in the kidney at a later time — just prior to death.

(1) Cohnheim: "Vorlesungen über Allgemeine Pathologie" 2nd Edn. 1832. 3d II. S. 326.
It is, in all probability, the result of the toxaemia produced by the, at present unknown, Scarlatina organism.

And this brings me to discuss the bacteriological work that has been done; for in this largely lies the raison d'etre of any prophylactic urinary antiseptic treatment.

**BACTERIOLOGY.**

The first researches were made to prove the inoculability of Scarlatina.

Stoll introduced some of the desquamated scales under the skin and reproduced Scarlatina.

Miquel injected blood collected from the immediate vicinity of a Scarlatinal area and obtained a red circle, which disappeared on the 5th. day. The subjects thus inoculated enjoyed immunity.

Leroy, on himself obtained the same results as Miquel.
Ashmed, more recently, has inoculated a young Jap with a little desquamated Epidermis from a child with Scarlatina.

Three days later, there was observed, at the point of inoculation, a fairly wide circle of Scarlatinal rash, intensely bright, surrounding the little central scab.

There was swelling of the tonsils with a whitish exudate.

There was no fever or desquamation, due probably to the fact that the Japanese do not readily take Scarlatina, and also because it was a very mild attack, on account of its having been introduced under the skin.

Many claim to have discovered the organism of Scarlatina.

Hallier in 1869 was the first to examine the blood. In it he found numerous micrococi which he called

Tilletia Scarlatinosus.

Caze, Feltz and Tschauer (1) found bacteria in the blood, the tissues, the products of desquamation and in the urine. But the inoculation of the blood into rabbits only produced a Septicaemia without any eruption. Klebs described under the name of Monas scarlatininosum what he thought to be the cause of Scarlatina.

Micrococci have been described by Riess in the blood serum, post-mortem, by Pohl Pinkus and Klamann in the mouth and scales of the skin; and by Crooke in the organs from uncomplicated Scarlatinal cases.

Birch-Hirschfeld, Gravitz and Cohnheim stated that they found microbes in the vessels of the kidney, and that they passed out into the urine, in persons suffering from infective processes.

(1) R. Wurtz in Fievres Éruptives (Traité de Médecine 1805).
In 1880, Klebs, Letzerich and Bouchard stated that albuminuria of specific fevers was associated with the presence of bacilli in the kidney. But some organisms, which are poisonous to the animal, e.g., Jequirity bacillus and Anthrax bacillus in the guinea-pig and sheep may escape into the urine without causing any apparent renal mischief. This may depend upon differences in the structure of the glomeruli in individuals of different species or of different races e.g. Teutonic and Mongolian, or of different age-periods. Or, more probably, some predisposing cause weakens the power of resistance, and thus provides a suitable soil in the kidney or elsewhere for the organism or its toxines to work mischief.

In 1885 Klein obtained a streptococcus from the vesicles on the teats, and from the tissues of cows, to which Power had traced the infection in the
Hendon epidemic of 1885.

And he stated that the organism had the same morphological and cultural characters as those of the streptococcus, which he obtained from the blood and tissues of patients suffering from Scarlatina.

And, moreover, when injected into calves, guinea-pigs or mice, he stated that it brought about symptoms analogous to those produced by Scarlatina in man. (1)

In 1890 Klein injected his Scarlatina streptococcus into recently calved milk cows and found that visceral and teat eruptions were produced identical with those above referred to.

These conclusions of Klein and Power were opposed by Crookshank, and also by a Commission of Inquiry appointed by the Edinburgh Medico-Chirurgical Society.

(1) Klein: "Natural History of Scarlatina."

Jamieson and Edington (1) in 1887 found a mobile bacillus which only appeared after the third week of the disease, never before. But they found it in all their artificial cultures from a drop of blood of a Scarlatina patient, provided the blood was taken on the third day of the fever, never after. This appears to be rather contradictory. They injected this Bacillus Scarlatinae, as they called it, into guinea-pigs, rabbits and calves, and produced an Erythema followed by desquamation. These researches have not been confirmed, and have been opposed by Longhurst and Smith, who consider it to be an ordinary septic bacillus of the sweat.

MM. d'Espine and de Marignac (2) have isolated from the blood of Scarlatinal persons a streptococcus presenting characters different entirely from

11th. June 1887.

(2) D'Espine et de Marignac: Arch. de med. Exp.1892,
p. 488.
those of the known Streptococci.

Many eminent observers, such as, Löffler, Heubner and Sartor, Fraenkel and Freudenberg, Babes, Crooke, Raskin, Wurtz and Bourges, de Marignac and d'Espine have shown that in the secondary complications the causal organism is *streptococcus pyogenes* alone, but sometimes associated with the *pneumococcus*, *staphylococcus albus* and *aureus*, *bacillus coli* and other septic bacteria.

Baginsky found it constantly in 686 cases of Scarlatina, usually associated with other microorganisms.

But this streptococcus is rare in the blood of Scarlatina patients, and Raskin and Babes have never found it in the skin.

C.J. Lewis (1) has recently studied the discharges from Scarlatinal patients, and comes to the following conclusions:

(1) C.J. Lewis: Medical Press and Circular Apr. 11th. 1906 pp. 388 - 91
That there are 4 main groups of organisms present, viz.,

1. Pneumococci.
2. Staphylococci.
3. Streptococci.
4. Diphtheroid bacilli.

Pure cultures of any of these he found to be the exception.

In the aural suppuration he found most frequently pneumococci, streptococci pyogenes and "bacilli of the diphtheria group".

In the nasal suppuration the order is streptococci, staphylococci and Pneumococci.

When injected into guinea-pigs and rabbits, he found them more virulent in the later stages of the disease, as one would expect.

A very interesting point is, that he found that the streptococci from the Rhinitis of Scarletina may retain their pathogenicity when the discharge has lasted for more than a month.

And he therefore suggests that Rhinitis may be the
most fruitful source of return cases.

I have gone more fully into these cases than I otherwise would have done, because the observations were made quite recently on patients, who were being treated in the Edinburgh City Hospital, and were therefore under the same general conditions, as the cases to which I shall refer later.

As to whether the streptococcus is itself the cause of Scarlatina, the two following hypotheses have been suggested: (1) Berge (1) suggests that the streptococcus localised in the tonsils may secrete an erythrogenic substance which produces the eruption.

And Jaccoud (2) has noted the possible coincidence of Erysipelas and Scarlatina. Still we know that the streptococcus can produce a true erythema without there being any Scarlatina. And this seems to be

(1) Berge: Soc. de biol., 16 décemb. 1883. Th.de Paris, 1885.

(2) Jaccoud: Erysipele et scarlatine (Gaz.des hôp., 18 juin 1891).
at present on the horizon of theory.

2. The second hypothesis, propounded by Babes, is, that it is due to one particular variety of streptococcus and not to a common streptococcus.

He found in the breast of a Scarlatina patient a streptococcus in long chains of diplococci, somewhat flattened; it is slightly virulent for the rabbit. Kurth (1) described a streptococcus, which he called "conglomeratus", as the cause of Scarlatina.

It is different from other streptococci, morphologically, and by the nature of its culture in bouillon.

But from the same scarlatina patient one can obtain, by culture, different kinds of streptococci.

All Scarlatina patients do not give the same form of streptococci.

It is probably identical with the streptococcus described by Rosenbach,

Löffler and Fehleisen.

Lenharz, Raskin, Widal and Bezançon (1) after numerous researches on the streptococcus of the mouth accepted this view.

Since 1897 Moser (2) has cultivated a streptococcus from the postmortem heart's blood of Scarletinal cases in 63 out of 69 cases, and twice from the cerebro-spinal fluid of the living subject.

But Moser himself and others have shown that the serum of Scarletina patients does not agglutinate the streptococcus.

Besredka and Dopter (3) are of the opinion that the streptococcus is not the cause of Scarletina.

Pearce (4) states that the secondary inflammatory lesions are due to:

a. Streptococcus pyogenes.

b. Staphylococcus pyogenes aureus.

c. Pneumococcus.

(2) Moser: Ueber die Behandlung des Scharlachs m. einem Schar. Streptokokkenserum. 1903.
(4) Pearce: Boston City Hosp. Reps 1899.
and he puts them in that order of frequency. Streptococci he found most frequently in the nose and throat.

Baginsky (1) states that it is difficult, after his experience, to recede entirely from the position that Scarlatina is due to a streptococcus, and that the latter by no means represents a secondary infection following in the wake of some other germ disease.

He read the paper before the Berlin Medical Society, and in the discussion, Heubner admitted the constant presence of streptococci, but was not satisfied with the results of animal experiments. And Slawyk had failed to find this organism at the beginning of the disease in some cases. Wassermann stated that if Baginsky is correct Scarlatina is always a septic process.

Class (1) holds that the Diplococcus Scarlatinae is the cause.

He states that he found it invariably present in the throat secretions, blood and scales.

He declares that it possesses an individuality, which differentiates it from all other organisms. It is pathogenic to experiment animals, and a disease is produced in the pig by it, which closely resembles human Scarlatina.

He, moreover, states that the blood of Scarlatinal convalescents inhibits the growth of this organism. And it is capable of causing Nephritis in guinea-pigs.

He adds that the injection of convalescent Scarletina blood into an experiment animal apparently protected it against the disease.

The greater number of those who have made bacteriological research as to the cause of Scarlatina may be divided into camps.

Klein, Babès, d'Espine, Soerensen, Glass, Baginsky, Sommerfeld, Hlava and Moser are of the opinion that in all probability Scarlatina is due to a true coccal infection -- diplococcal or streptococcal, according to taste, whereas, Crooke, Fraenkel, Raskin, Heubner, Marmorek and Slavyk attribute it to an unknown Virus.

After the researches of Babès and Raskin, it is suggested that Scarlatinal Nephritis, like the Tonsillitis and Otitis, is set up by a streptococcus. Babès found it in the Kidney in 26 out of 30 cases of Scarlatinal Nephritis, and Raskin found it several times alone or along with a diplococcus.

A case reported by Juhel-Renoy (1) is of distinct interest.

(1) Juhel-Renoy: Arch. gén. de méd., 1836.
The patient died on the seventh day of the disease with well marked Nephritis and Anuria.

At the autopsy infarcts of the kidney were found caused by Emboli formed of microorganisms. They were found in the vascular loops of the Glomeruli.

There were no other lesions in the kidneys, and the uriniferous tubules were permeable.

If the kidney is irritated by the organism or toxine of Scarlatina, whatever it may be, then there is a weakening of the powers of resistance, a local lowering of the vitality of the tissue affected, and so a permeability or break in the line of defence, and thus a suitable soil produced for a successful attack, at a later period, by the streptococcus, or whatever it is, that causes Nephritis.

But there are doubtless many determining factors in the prevalence of Scarlatinal Nephritis such as,
errors in diet, a chill in the period of desquamation, the influences of race, sex, season, atmospheric conditions, social conditions, and more especially age, and the type of the epidemic. Although these would probably not of themselves produce Scarletinal Nephritis, yet some of them may be looked upon as exciting causes and must therefore be considered.

Desquamation and its relation to the causation of Nephritis.

If severe desquamation played an important role in the causation of Scarletinal Nephritis, one would expect to see it early, and associated with early albuminuria, or late, with Nephritis.

I had only one case of severe desquamation associated with Nephritis. He was a Shetlander of 19 years of age, who on account of his work had extremely thick skin on his hands and feet. On the 10th day of the disease, his hands desquamated as if he had taken off
a pair of gloves, and on the next day he developed albumin in his urine, which, previous to this time, had been quite clear.

And two days later (13th. day of the disease), blood and renal casts were found in the urine.

But this case was an exception; my other 25 Nephritis cases desquamated no more markedly and no earlier or later than those who did not have Nephritis.

In fact, a female patient, 21 years of age, showed extremely severe desquamation with widely distributed minute pustules immediately beneath the skin, which latter caused a high swinging septic temperature up to 104 degrees Fahrenheit and which did not settle until the 21st. day of the disease.

Yet, during the whole course of the disease, she had only the merest trace of albuminuria on the 2nd. and 4th. days of the disease, and exhibited no late albuminuria or Nephritis.
So that my experience has been that desquamation, per se, has very little to do with the causation of Nephritis.

Some years ago it was a practice in a part of Lincolnshire to rub oil all over horses that had been clipped and singed, but it was discontinued, as several of them died, it was said, of Nephritis or of Pneumonia.

And it is known that rabbits, when varnished, have been found to die.

But this is too artificial a comparison; for desquamation, however severe, can never impede the excretory action of the skin to such an extent as oil or varnish.

Bartels (1) did not believe that the skin affection had anything to do with the causation of Nephritis;

(1) Bartels: Allgemeine Symptomatologie der Nierenkranckheiten. S.222.
for he found that Nephritis did not accompany far graver alterations of the skin, following quite as acute and febrile a course as Scarlatina. In his opinion the frequency of Scarlatinal Nephritis was due solely to the character of the epidemic.

He had 22 cases of Nephritis in 180 patients treated by him in 1853-4, and 13 out of 84 patients in 1863, and out of 100 patients at other times, he met with scarcely a case of Nephritis.

Five out of the 22 cases in 1853-4, and all of the 13 in 1863 died.

And he therefore concluded that the intensity of the Nephritis varied with the epidemic.

He considered that the Nephritis was independent of chilling; for children treated in bed with every care might get it, whereas other children who had attended the Poliklinik and passed through their illness, so to speak, on the streets, frequently escaped.
He concluded emphatically that it was a specific inflammation.

**Seasonal influence.**

There is something peculiar to the months of *October* and *November* that is particularly suitable to the growth and spread of the Scarlatina virus, and the increase of the complications, more especially *Nephritis*.

Hirsch collected reports from 435 Scarlatina epidemics in the average latitudinal distribution, and out of the 100 epidemics:

- 29.5 per cent were in the Autumn.
- 24.7 per cent were in the Winter.
- 24.0 per cent were in the Summer.
- 21.8 per cent were in the Spring.

The severity of the Autumn epidemics is well illustrated in the following table, comparing the percentage mortality in London and Sweden in the different seasons.
Deaths in London from 1838 to 1863 = 55,287.

" " Sweden " 1864 to 1873 = 11,630.

<table>
<thead>
<tr>
<th>Town</th>
<th>Year</th>
<th>Cases</th>
<th>Deaths</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hamburg(1)</td>
<td>1881</td>
<td>2902</td>
<td>133</td>
<td>4.6</td>
</tr>
<tr>
<td></td>
<td>&quot;</td>
<td>1886</td>
<td>3105</td>
<td>348</td>
</tr>
<tr>
<td></td>
<td>&quot; 1885-1884</td>
<td>21,834</td>
<td>1475</td>
<td>6.8</td>
</tr>
<tr>
<td>Stockholm(2)</td>
<td>1865</td>
<td>2019</td>
<td>56</td>
<td>2.8</td>
</tr>
<tr>
<td></td>
<td>&quot; 1869</td>
<td>1190</td>
<td>327</td>
<td>27.5</td>
</tr>
<tr>
<td></td>
<td>&quot; 1865-1866</td>
<td>15,137</td>
<td>2461</td>
<td>16.3</td>
</tr>
</tbody>
</table>

The importance of the severity and character of the epidemic.

There is a great changeability in the severity and character of different epidemics, as is well seen in the following statistics.
Thus the Scarlatina in Hamburg in 1866 was very severe, having nearly 5% above the average mortality percentage.

And the Stockholm statistics are even more striking; the virulence of the epidemic of 1869 is in strong contrast to that of the year 1865.

The frequency in a given time and the extensiveness of the epidemic have no definite relation to its severity.

In England (3) the mortality has varied from 13% to 40%.

(1) Hamburg: Bericht des Medicinalrats (Dr. J. Reincke) über die Medicinische Statistik des Hamburger Staates für das Jahr 1894.

(2) Stockholm: Quoted by Sture Carlsson from Lennmalm: "Nagra anteckningar om Skarlnakansfebern pa Katarina Sjukhus." 1895.

(3) Moore: Eruptive and Continued Fevers. Dublin 1892.
Sporadic cases are as dangerous as those in the epidemic form.

Thus out of 11 cases, in the year 1868 in Stockholm, 5 died.

**Influence of Age on Nephritis.**

It is a remarkable fact that nearly all the cases of Scarlatinal Nephritis occur between the ages of 3 and 8.

It is true that the great majority of cases of Scarlatina occur in this age period, but the Nephritis percentage is too high to be explained away by the greater preponderance of cases between these ages.

Is it that there is a subtle physiological change taking place in the kidney in this age period, which renders the organ more liable to be inflamed? That the children are of a tender age, does not explain it, for infants are remarkably insusceptible to Scarlatinal Nephritis — in fact, to Scarlatina altogether.

Every year after the age of 10, persons become
much less liable to Nephritis. These points are
well brought out in Tables 6, 7 and 8. (pp 95, 96 and 97)

The Registrar-General in his Annual Report for 1886
made calculations, which are based on nearly half a
million deaths from Scarletina in England and Wales
in the period 1859 to 1885, also on the case mortality
among 17,786 scarlatina patients admitted during the
12 years 1874-1885 into the London Fever Hospital
and the Metropolitan Asylums Hospitals at Stockwell
and Homerton, and also on nearly 5000 cases of Scarlatina in Christiania from 1870-82, and on the returns
of all known cases of Scarletina for some large towns
in England in which notification of infectious
diseases has been for some years compulsory.

His conclusions, which show that both age and sex
have influence are as follows:

1. the mortality is at its maximum in the 3rd. year
   of life and after this diminishes with age, at
   first slowly, afterwards rapidly.
2. This diminution is due to three contributing causes:

(a) The increased proportion in the population at each successive age-period of persons protected by a previous attack;
(b) the diminution of liability to infection in successive age-periods of those who are as yet unprotected;
(c) the diminishing risk in successive age-periods of an attack, should it occur, proving fatal.

3. The liability of the unprotected to infection is small in the first year of life, increases to a maximum in the fifth year or soon after and then becomes rapidly smaller with advance of years.

Cases in the first year of life are but few.

4. The chance that an attack will terminate fatally is in infancy, and diminishes rapidly with years to the end of the 25th year; after which an attack is again somewhat more dangerous.
Influence of Sex.

5. The female sex throughout life, the first year possibly excepted, is more liable to Scarletina than is the male sex.

6. But the attacks in males, though fewer, are more likely to terminate fatally.

7. Hence the longer an attack is deferred, the less likely it is to occur at all, and the less likely it is to end fatally.

Why should the infant show an immunity from Scarletina?

Is the virus so quickly eliminated through the kidneys, bowels and skin that it cannot cause a perceptible reaction?

Perhaps the pabulum is unsuitable, and the phagocytes too formidable.

There is little doubt that the virus does enter the babe of the nursing mother who has contracted Scarletina.
The social standpoint.

Children of the better classes are less often fatally affected, but they appear to be as liable to contract Nephritis as those of the poorer classes. And experimentally, Fodor found that certain bacteria injected into an animal reduced by hunger and cold, are better able to thrive than they are when injected into the animal when in good condition. Perhaps changes of constitution dependent on season and climate exert their influence. But it is more probable that the virus itself becomes more virulent in October and November and feeble again in January.

As to the influence of the weather, atmospheric pressure and altitude, nothing definite is known. We may readily suppose that the atmospheric conditions act on the virus or on the host, just as
the dry cold atmosphere is detrimental to the growth of the Tubercle bacillus; so there may be something suitable to the virus in the atmospheric conditions of October.

Dr. Ballard (1) found that the extension of Scarletina was favoured "by a temperature above the average for the season and that a dry state of the atmosphere, with little rain, favoured its spread more than the reverse condition".

He found the disease in the Autumn "most prevalent in the years when the seasons on the whole were warm and rainy".

And Longstaff (2) says of "Scarletina and certain other diseases" in England and Wales as to their relation to the rainfall at Greenwich, says: - "the seasonal prevalence of these diseases is not at


(2) Longstaff: " " " " 1880.
all obviously related to the rainfall.

And he also says that there is an inverse relationship between the mortality curve and the amount of rain, and also the number of days on which it falls; and he assumes that the frequent fall of rain purifies the air of contagion.

**Blood Examination.**

The examination of the blood in Scarlatina has not as yet proved of much value.

Widowitz noticed that when Nephritis appeared as a complication, the Haemoglobin gradually diminished with its appearance or suddenly diminished in the event of an exacerbation of the Nephritis.
Conclusions as to the Causation of Nephritis.

The conclusions that I feel justified in forming as to the causation of Scarlatinal Nephritis are:-

1. That it is in all probability the result of an irritation caused
   (a) by the organism of Scarlatina itself,
   (b) or by its toxines.

2. That it may be the result of a secondary streptococcal invasion, the success of which has been promoted by an irritation, and a local weakening of the powers of resistance on the part of the renal tissues and so providing a suitable soil for an invading organism.

3. That the exciting cause may be one, or a combination, of the many influences capable of lowering the vitality and the powers of resistance on the part of the individual, as a whole, such as errors in diet, chilling in the desquamative period, etc.
The various methods that have hitherto been employed as a prophylaxis against Scarlatinal Nephritis.

Ever since Scarlatina was a recognised Entity, physicians have been endeavouring above all things to avoid the advent of Nephritis.

Milk diet of some form or other has for a long time been a recognised form of treatment.

The object being to give as much food as is required, with the minimum of work for the Kidneys.

But milk only, is too bulky and is apt to produce dropsy, therefore it is well to add farinaceous puddings, and this, with plenty of water, barley water or lemonade, is the staple diet for the first three weeks.

Fish and chicken are given in the 4th. week.

Jaccoud (1) looks upon milk as a preventive of Nephritis in Scarlatina.

Great care should be taken until desquamation is over.

Patients should be kept in bed for the first 3 weeks and it is safer to keep the children from playing out of doors for the first 5 weeks.

This I may say has been practically the routine practice observed in the cases to which I shall later make reference.

There should be plenty of air-space ventilation and light.

The temperature of the room should not be above 60 °F and the patient should not have on many bed-clothes.

**Oil of Eucalyptus.**

Curgenven (1) gives the experience of Priestley and others in the Eucalyptus oil inunction and says that the complications are fewer, the duration of the fever less, and the disinfecting power great, and that the disease is prevented from spreading.

Vierodt (1) has great faith in this treatment.

Hydrotherapy.

On the principle of stimulating the circulation and thus producing a more vigorous flow of blood through the kidney, and also by mechanically removing the surplus skin during desquamation, and also by permitting the sweat glands to act more freely, bathing and sponging are recommended.

Hydrotherapy is practised, chiefly in Germany, from the very beginning of the disease, and Nephritis is said to be lessened by it.

Buxbaum commences his treatment by sponging all over the body with a cloth that has been dipped in cold water, to gain the patient's confidence.

If the pulse becomes slower and stronger, the "half-bath" with friction and affusion is given two or three times.

(1) Vierodt: "Behandlung des Scharlachs" in Pentzoldt - Stintzing's "Handbuch".
three times daily depending on the effect.

If the patient is stuporose or exhibits convulsions, warm baths with cold affusions are given.

Thomas (1) says he found a reduction in his Nephritis cases after commencing hydrotherapy in Scarlatina.

Schill (2) of Wiesbaden treated 110 successive cases of Scarlatina with hydrotherapy and only 1 patient developed Nephritis.

The following are the recommendations given.

The height of the patient's temperature is taken as the guide.

Bathe when the Rectal temperature is 104 °F.

For young children, the temperature of the water should be 68 °F and the bath should not last more than 5 minutes.

(1) Thomas: Ziemssen's Cyclopaedia.

(2) Schill: Nothnagel's Encyclopaedia of Practical Medicine.
Older patients may have the water at 59 °F for 5 minutes.

Dry the patients quickly and put them to bed.

Repeat every 4 or 6 hours.

If the case is mild, fewer baths are required.

If the patient's temperature does not reach 104 °F, a lukewarm bath or even sponging is all that is recommended.

And, in the febrile excitement that appears towards evening at the beginning of the disease, cold sponging or the half-bath is recommended.

But Jürgensen (1) says in mild epidemics the above measures are absolutely unnecessary.

Leichtenstern (2) speaking in favour of Hydrotherapy says: - "my statistics, based upon a very large supply of material, justify me in the conclusion that

(1) Jürgensen: Nothnagel's Encyclopaedia of Practical Medicine.

(2) Leichtenstern: " " " " " " 
the cold water treatment of Scarlatina markedly diminishes the tendency to Nephritis as a sequel, rather than increases it".

Contra - indications.

If gangrene be present or if there is marked septic intoxication.

If there be Bronchitis, give a warm bath with a cold douche.

In cardiac weakness.

If there be any signs of dyspnoea with partial occlusion of the upper air passages.

If there be any haemorrhage or a haemorrhagic history.

If there be any inflammation of the joints.

The epidemic, in which my cases appeared, being of a mild type, I cannot speak from any personal experience of the value of hydrotherapy.

But I found that in cases with high temperature, sponging had a very quieting and soothing effect.
Crede's ointment.

Baginsky (1) tried Crede's colloidal silver ointment in some severe cases with a view of antagonising the septic element in Scarlatina.

But only 3 out of his 13 cases survived, and it failed to prevent Nephritis, otitis media, etc. The very idea of using an ointment in Scarlatina seems to be incorrect.

Serotherapy.

If the Nephritis be due to organisms, or their toxins circulating in the blood, and eventually being excreted by the kidneys, serotherapy has a great future before it.

But little has been done as yet.

In 1896 Josias of the Trousseau Hospital gave an account of the experience of that institution with Marmorek's anti-streptococcal serum.

The results were disappointing.

And in comparing two series of cases, in one of which the serum was employed, appears to show that the latter offers no advantages over a regimen of milk diet and antiseptic lavage of the throat.

**Moser's Serum.**

Moser of Wien prepares a "Scharlach-streptokokken-serum", by first obtaining as soon after death as possible, the blood from the heart of a patient who has died of Scarlatina. This is mixed with the bouillon and is injected into a horse, and when the horse is recovering from the attack, its blood is taken and the serum separated from it for the treatment of Scarlatina patients.

I had the opportunity of seeing this treatment carried out in Professor Escherich's Klinik, at the St. Anna Kinderspital, Wien, when I was there for 3 months in the summer of 1905.
The serum costs about 16/ per injection of 100 cubic millimetres.

It is given to the severe cases only.

Children of 3 years usually get 100 cubic millimetres, whilst those of 6 and upwards, get 200 cubic millimetres.

It is injected into the loose cellular tissue of the lower part of the abdomen.

The quantity is large and the injection of it is therefore painful, but none of the cases that I saw injected gave any trouble afterwards at the seat of injection.

I remember two brothers, Michael V., aged 3 years, who was not nearly so ill on admission as Stefan V., aged 6 years.

The latter was injected with 100 c.M. and made an excellent recovery, though his temperature was 105 F and he was acutely ill.

His brother Michael V., was not so ill and consequently was not injected, but his Fauces instead of improving got worse, and he was quite an invalid when Stefan was convalescent.
They were treated in the same ward.

Three other very severe cases in children of 3, 10 and 12, I remember, made excellent recoveries with no sequelae.

So that, unlike Josias's experience with Marmorek's serum, I think Moser's serum is beneficial in the treatment of very severe cases, and it certainly did no harm to the five cases in which I saw it used.

However, it is not yet on the market, I believe, so that its field of action is limited.

Preventive inoculation.

Stickler (1) attempted to produce a mild type of Scarlatina by inoculating children subcutaneously with mucus from the throats of recent Scarlatina patients.

But the type of disease he produced was too severe to attempt securing immunity in that manner.

But he proved that the secretions of the mouth and pharynx, at the beginning of the disease, are very virulent.

There was hardly any incubation period; the temperature rose within 2 hours and the rash within 24 hours of the infection.

The injection of the blood serum of Convalescents

Roger (1) reported a case of a Scarlatina patient becoming comatose on the second day of the disease. Hydrotherapy and saline infusions were tried with no improvement. And death seemed imminent.

But he quickly prepared a serum from the blood of a convalescent Scarlatina patient. The patient himself was first bled and then the serum of the Convalescent patient, 80 c.c., was injected into a vein.

The patient rallied in 5 hours.

Then cool baths were resumed and eventually the patient made a good recovery.

One cannot generalize on one case, but the report of this one is distinctly encouraging.

**Diuretics.**

A healthy increased flow through the kidneys should be aimed at by allowing plenty of non-irritating fluid to be taken. If, however, there are evidences of commencing Nephritis, Potassium Citrate and Diuretin (theobromin-sodium salicylate) given in 10 - 15 grain doses will do good, by counteracting the tendency to dropsy; and moreover their marked diuretic action will stimulate the kidneys to excrete the virus without irritating them.

I found that Urotropine, Hexamethylene-tetramine and Metramine all had a slight diuretic action.
Diaphoretics.

It is well to encourage the skin to act by frequent tepid sponging and occasional tepid baths, and to let the patients sleep between the blankets, if they have shown early albuminuria, but unless Nephritis develops it is not necessary to give drugs e.g. Tinct. Jaborandi.

Purgatives.

Only if Uraemia threatens, or if dropsy has begun to develop is it advisable to use purgatives. But if they become eventually necessary, Magnesium Sulphate is the best to use. The purging must not be sufficient to lower the arterial tension, or else diuresis is checked.
Urinary Antiseptics.

In addition to the older urinary antiseptics, such as Benzoic Acid, Salicylic Acid, Salicylate of Soda, Salol, Uva Ursi, Copaiba, Cubebs, Sandalwood oil and many other volatile oils given to prevent decomposition of the urine, a whole host of new drugs have within recent years made their appearance.

The maker of each drug, naturally enough, like the mother with her new baby, sees charms in the offspring, which others are not so willing to allow.

But as the test of good music is the length of time it lives, so is it with drugs.

Fashions for new drugs come and go, but a good one is never out of fashion. And Urotropine is one of these.

Since it was brought into prominence in medical practice by Professor Nicolaier in 1894, many variations of the same thing have arisen, e.g. Cystamin, Uritone, Aminoform and Metramine.
Helmitol and New Urotropine are combinations of
Urotropine with Anhydromethylene Citric Acid.
The New Urotropine contains 40.7 per cent of Urotropine, and if sugar be added to a solution of it, it
effervesces and makes a pleasant lemonade.
If the urine be acid it does not act so well as the
parent drug.

Griserine was tried by Küster of Berlin and found
to have an antiseptic action in the bladder, and he
has lately (1) recommended its use in Phthisis
Pulmonalis.
But as it is very apt to cause painful diarrhoea, it
has not been much used.

Hetraline contains 60 per cent of Hexamethylene-
tetramine in combination with a Phenol derivative.
It is dioxybenzoyl- Hexamethylenetetramine.
It is probably the best of the very newest

(1)
1906.
urinary antiseptics, but it has yet to be proved that it has an equal footing with Urotropine.

**Hexamethylenetetramine.**

This drug was first produced in 1860, by Butlerow, by passing dry Ammonia gas over powered dioxymethylene.

And it was described by him as Hexamethylenamin.

And it was he who also applied the name Hexamethylenetetramine to it.

This latter name is the better of the two, because the number of atoms of Nitrogen contained in the molecule is expressed by it, and confusion is also avoided with the liquid of the formula

\[
\text{C}_6\text{H}_{12}\text{N}_2\text{H}_6
\]

which is prepared from Hetchexahydrobenzol, a colourless preparation which smells strongly of Conium, is slightly soluble in water, and which Baeyer justly describes as Hexamethylenamin.
In 1862 A.W. Hofmann showed that Hexamethylene-tetramine is also formed when Formaldehyde is vaporized in the presence of an excess of ammonia. But as the production of large quantities of Formaldehyde is a matter of little difficulty, the drug which now goes under the name of

**UROTROPINE**

is very simply prepared in the following manner, as described by Professor A. Nicolaier (1):

Formaldehyde vapour is passed into concentrated ammonia, the slightly ammonia-alkaline liquid being steamed into syrup; this is received in hot alcohol, from which Urotropine crystallizes out.

The transposition which takes place is shown in the following formula:

\[6 \text{CH}_2 \text{O} + 4 \text{NH}_3 = \text{C}_6\text{H}_{12}\text{N}_4 + 6 \text{H}_2\text{O}.

According to Tollens and Moschatos the formula is:

\[\text{C}_6\text{N}_{12}\text{N}_4 \square (\text{CH}_2)_6\text{N}_4\].

The name Urotropine (Τὸ ὄρπον, the urine; τρέπειν, to change) was given to Hexamethylenetetramine by Professor Nicolaier of Göttingen, who introduced it into medical practice in 1894.

The directions given by the "National Dispensatory" for the preparation of hexamethylenetetramine are very similar to those I have just quoted, and are as follows:

"To 100 parts of 40 per cent Formaldehyde add in small quantities of the stronger ammonia water, keeping well cooled, until after standing some hours it smells strongly of ammonia; set aside for 12 hours and crystallize from shallow vessels, purify from animal charcoal and recrystallize".

Netramine is prepared in a precisely similar fashion, but the proprietors claim that it is recrystallized once oftener than Hexamethylene-tetramine.
Chemical and Pharmacological properties of Urotropine.

The crystals are colourless, shiny, transparent six-sided rhomboids or prisms which, if kept dry, do not decompose, according to Moschatos.

If pure, it is odourless: When heated it gives off an unpleasant odour like sea-weed.

It is readily soluble in cold water.

Its watery solution is slightly alkaline and gives off Formaldehyde on heating, even at a temperature as low as that of the body.

Therefore, therapeutically, it should not be given in warm water.

It has at first a rather pleasant, sweetish taste, which afterwards becomes somewhat bitter.

The hydrolytic decomposition of Urotropine into Formaldehyde and an ammonium salt takes place in the kidneys, ureters and bladder, and probably also in the blood.

It becomes hydrolysed into the two substances from which it was derived.
The following formula represents this hydrolytic decomposition:

\[
\text{C}_6\text{H}_12\text{N} + 6\text{H}_2\text{O} = 6\text{C}_2\text{H}_4\text{O} + 4\text{NH}_3.
\]

Soon after its introduction, Urotropine was found to be very valuable in checking the decomposition of the urine in ammoniacal cystitis, the effect being due to the liberation of Formaldehyde from the drug at the body temperature.

It begins to be eliminated about 15 minutes after administration and can be found in the urine after the lapse of a day or two.

It does not render the urine alkaline and therefore causes no precipitation of phosphates.

The great value of the drug lies in the powerful antiseptic properties of Formaldehyde, which latter in a solution of 1 in 10,000 has a bactericidal effect (1)

(1) Lancet. 7th. April 1906.
The administration of Urotropine, Hexamethylene-
tetramine and Metramine.

I have experienced no difficulty in giving these
drugs to patients whose ages varied from 18 months
upwards.

It is best to dissolve the powder in cold water
and give the solution along with plenty of milk
or water.

As they have a sweetish taste at first, children
take them readily.

Some of the younger children did not like the
powdered form, but showed no evidence of disapproval
for the aqueous solution.

They also did not approve of the innovation of
administering drugs in the tabloid form.

Single large doses of Urotropine of 90 to 120
grains are borne well by the system and some
patients can take 60 grains daily with no inconven-
ience, and although Windell, Casper, Tanago and
Brewer have given 60 grains daily for a lengthened
time with no ill effects, Nicolaier recommends
more care.
Wilson Parry (1) attributes an irritation of the bladder to Urotropine, and suggests that it may also irritate the kidney.

His was a case of a man with enlarged prostate and with alkaline foul urine.

After administering 30 grains daily for about 26 days, though the state of the urine was immensely improved, the amount of albumin in the urine was increased, and the patient complained of pain in the bladder.

And after stopping the Urotropine, the albumin was reduced considerably, and the vesical irritability disappeared.

This, however, is only an odd case, and much stress should not be laid on it, as against the overwhelming evidence of numerous competent observers.

He moreover did not state whether he administered it with a large quantity of fluid, which is an important point.

At the same time that he was giving Urotropine, he was washing out the bladder daily with an antiseptic.

And therefore it is quite within the realms of possibility that he blamed the Urotropine, when the antiseptic washing out was really at fault.

However that may be, I can truly say that my experience has been very different.

Out of 47 consecutive cases on Urotropine, not one had Nephritis, and only one developed albuminuria, and none of them complained of kidney, vesical or urethral discomfort.

The results of the cases treated with Hexamethylene-tetramine and Metramine are not so striking, but conform practically to the average case of Scarletina.

I shall refer to these more in detail later.

But I must remark here that out of my 133 cases treated with Hexamethylene-tetramine, 6 experienced a slight burning sensation in the bladder and urethra. In no case was it severe enough to cause the discontinuance of the drug, and when given with more fluid the irritation entirely disappeared.
In none of the 8 cases did Nephritis develop, nor
was the albumin increased, at the time this symptom
was present, in those which had albuminuria.

Metramine with its 26 consecutive cases had none in
which this slight vesical and urethral
irritation was present.

Experiments with Urotropine.

Experimentally, (1) albuminuria has been seen in
rabbits after single doses of 150 grains.
And Haematuria was produced in dogs after 225 grains;
both conditions were temporary.
Biss, who reports these experiments, states that in
doses of 5 grains thrice daily, it does not actually
kill Typhoid Bacilli, but prevents their growth in
the urinary tract, and does not irritate in such
small doses.

Dosage.

The dose I employed with all the three drugs, Urotropine, Hexamethylenetetramine and Metramine, was 5 grains, thrice daily, after food.

The drugs were started on admission and continued, without interruption, except where Nephritis occurred, until the 28th. day in hospital, and as the great majority were admitted on the third day of the disease, they received the drugs up to the 31st. day of the disease.

I did not vary the dose, because the difference in the patients' ages supplied sufficient variety, and by consistently maintaining the same dosage, statistical comparisons are of more value.

I chose a small dose on the advice of Nicolaier, the introducer of Urotropine, who recommends that not more than 22 grains be given daily.

The great point to be observed is to well dilute the dose.
Houbner after prolonged use of Urotropine in children in the Charité Spital, Berlin, has seen no injurious effect produced on the alimentary or nervous systems, nor were the heart or kidneys deleteriously influenced.

Even when renal disease was present, it was not aggravated.

Richardson (1) has shown its marvellous effects when administered in cases of Typhoid Bacilluria and Cystitis.

It however has little effect on the acid Cystitis produced by Bacillus Coli Communis.

Horton Smith, in the Goulstonian Lectures of March 1899 drew attention to the wonderful bactericidal effect of Urotropine in Typhoid Bacilluria, and found that in some cases 60 grains was sufficient to permanently free the urine of the Typhoid Bacilli.

But as much as 210 grains had to be given when it was administered intermittently, that is to say,

(1) Richardson: Jour. of Experimental Medicine 1899.
given for two or three days and then three or four
days being allowed to lapse before the recommencement
of the drug.
He says:— "So marked and immediate, indeed, is the
effect of the drug, that, if the urine is not clear
at the end of the 24 hours, we may at once suspect
most strongly that the bacillus present is not the
Typhoid Bacillus, but one of the varieties of
Bacillus Coli. He advises its continuance for at
least a week.

As the patient frequently has bacilluria and is
unaware of it from subjective symptoms, Richardson
has suggested that all cases of Typhoid Fever
throughout the whole course and during the first
3 weeks of convalescence should be given 10 grains
of Urotropine thrice daily, with the intention of
preventing cystitis by the elimination of the
bacilli from the urine; and also from the Public
Health point of view for the prevention of the
spread of Typhoid.
The favourable results obtained by the use of Urotropine in Catarrh of the bladder, Pyelitis and Phosphaturia, due to the freeing of Formaldehyde in the ureters and bladder, prompted Widowitz of Graz to employ it as a prophylactic against Scarlatinal Nephritis. He adopted the general, and probably correct view, that Scarlatinal Nephritis is produced by an organism or by its metabolic products, and he says:—"I thought that, considering its well known properties, Urotropine might be of value."

Although Urotropine exercises no influence on the excretion of albumin in Chronic Nephritis, yet this did not prevent Widowitz from trying it in Scarlatina, as the conditions in Scarlatinal Nephritis are quite distinct from those of Chronic Nephritis.

In Chronic Nephritis anatomical changes take place which Urotropine cannot restore.
But when Scarlatinal Nephritis arises, the supposed bacteria are in full activity, and if this be counteracted by an effective local bactericidal agent, there would be a possibility of preventing the anatomical changes in the kidneys, and the appearance of Nephritis.

Widowitz (1) during 3 years, tried Urotropine in 102 cases of Scarlatina.

His procedure was as follows:

"A dose proportionate to the age of the child was given immediately on the commencement of the disease on 3 successive days, and was repeated during the 3 days beginning the third week, in which Nephritis is most frequently noted.

In this way, children of varying ages from 1 to 15 years and an adult aged 21, were treated.

0.05 to 0.50 gramme i.e. 7/8 gr. to 7/2 grains was given thrice daily.

The drug was always well borne and no injurious.

effects were observed.
Since introducing this treatment, I have not observed a single appearance of Nephritis in the whole of the 102 cases."

The frequency of Nephritis varies greatly with the type of the epidemic: Johannessen observed that it fluctuated between 16 and 90 per cent.
It is true that the great majority of the 102 cases of Widowitz's which occurred from 1900 to 1903, in Graz, were of a mild type.
But mild cases are almost as liable to develop Nephritis as the severer ones.
In severe cases, traces of albumin are frequently observed at the commencement of the illness, which is also true of any of the infectious fevers; and the albumin may suddenly disappear in a few days, when the temperature has dropped.
In Widowitz's cases the albuminuria quickly disappeared in each instance.
The number of his observations is too small to immediately look upon Urotropine as a prophylactic against Scarlatinal Nephritis, and the absence
of Nephritis in his cases might be a coincidence, but the fact that the 102 cases were unselected and that no Nephritis occurred after the use of Urotropine, is distinctly suggestive of the drug having some antagonising power against the, at present unknown, cause of the Nephritis.

Whatever the cause may be, it must have been at work before the onset of the Nephritis at the end of the third or the commencement of the fourth week of the disease.

And therefore if the antagonising treatment is to be of any value it must be started at the commencement of the disease.

It may be that the kidney through filtering so much toxic blood became at last exhausted.

Just as a Scarlatinal Otitis, Rhinitis or Adenitis may be a local breakdown, and an inability to throw off the virus, which is undoubtedly present in these three complications; for the two former
are the most fruitful sources of re-infection.
It has been seen time and again that a child has been kept in hospital for ten weeks, or even more, until the Rhinorrhea or Otorrhoea were cured.
The child may have even been put for a week in an Isolation Convalescent Scarlatina ward, as at present practised at the Edinburgh City Hospital, in order to take every precaution for the prevention of return cases.
The child is then sent home, and in the course of a week or so may develop a cold, with nasal catarrh, and a day or two after this, up comes the little sister to the hospital with a typical Scarlatina rash.
This must have been the experience of everyone who has been associated with a Fever Hospital.
What has been the means of infection?
The last visible signs of desquamation had long since faded away, every bit of clothing had been thoroughly fumigated and the child had had a
disinfecting bath before discharge from hospital.

Are we to suppose that at the end, say, of 5 weeks, the organisms which must have been widely distributed in the various tissues of the body, are suddenly going to fade away like "the baseless fabric of a vision, and leave not a rack behind"?

The organisms probably become inert and gradually disintegrate on account of the phagocytes and antibodies, and because they have run short of pabulum essential for their very existence.

Is it not conceivable that a nasal catarrh or an otorrhoea in late convalescence may form suitable soil for renewed activity for some of the organisms of Scarlatina which had lain dormant, and which on the advent of the nasal catarrh or otitis become active, and cast off in the nasal secretion or aural discharge and thus spread the infection: but which are not powerful enough to overcome the anti-bodies formed in the host's system to produce a second attack of Scarlatina?
If the feasibility of this theory be allowed, may not the same idea be extended to the Nephritis of Scarlatina?

And since the discharges from the Rhinitis, Otitis, unhealed suppurative Adenitis, and Vulvo-Vaginitis of Scarlatina are generally held to be very infective, why should Nephritis be allowed to pass unheeded on that score?

We have a strong suggestion for the possibility of this means of infection in comparing it with the bacilluria of Typhoid, which is a very real source of infection.

Because no one has yet demonstrated the organism of Scarlatina to the satisfaction of the scientific world, it does not follow that it is not abundantly present in the urine.
Buttersack (1) of Stuttgart advocates the use of Urotropine in SCARLATINA as soon as the faintest trace of albumin appears in the urine.

He remarks that it has not any ill-effects, even when recent kidney irritation is present.

I must say I think it is a mistake to wait till the albumin appears.

It is surely better to endeavour to combat the cause of the complication than to wait until the complication arises.

As no one can possibly predict which cases will have Nephritis and which will escape, I gave one or other of the 3 drugs already referred to, in every early case, on admission, except those cases that I kept as controls.

It mattered not whether the case were one of simple Scarlatina of a mild type, or a severe type of anginosa.

Cases of Scarlatina Maligna unfortunately do not live long enough for any prophylactic treatment to be carried out.

The only two cases of Scarlatina Maligna admitted into the City Hospital in the 5 months that I made my observations, died within 4 hours of admission.

I observe that recently Buttersack (1) has expressed the view that Urotropine should be given continuously, in view of the rapid elimination of Urotropine, from the first to the twenty-first or twenty-fifth day of the disease, which is the plan practically that I had already adopted in August 1905.

In a series of 35 cases he had no Nephritis, in a few cases, traces of Albumin suddenly appeared with a few hyaline and epithelial casts and epithelial cells from the kidney, but without oedema and with no alteration in the appearance, quantity or specific gravity of the urine.

(1) Med. Cor-Btl. d. Württemburg Arztl. Ver.,

As the result of the satisfactory account given by Widowitz of his 102 unselected cases of Scarletina with no case of Nephritis, K. Patschkowski (1) determined to treat his Scarletina cases with Urotropine in the Municipal Hospital of Charlottenburg, Berlin.

He gave it in 52 cases, which he says were of an extremely malignant type, resulting from an epidemic. 8 of these cases received Urotropine from 10 to 21 days continuously. Children were given 5 grains and adults 7½ grains thrice daily. In one case slight albuminuria appeared on the twenty-third and lasted till the twenty-seventh day, but with no casts.

In the other 44 cases, the patients received the drug thrice daily for 4 days as follows; on the 1st, 2nd, 3rd and 4th days, then again on the 8th, 10th, 11th and 12th days, and again on the 17th, 18th, 19th and 20th days after admission.

Most of the cases were admitted before the 3rd day of the attack.

Of these 44 cases, two developed Nephritis, one on the twentieth day and which lasted only four days, and the other one appeared on the twenty-second day and which showed a slight albuminuria on the fortieth day.

That is to say, only 2 out of 52 cases or 3.8 per cent had Nephritis.

Eighteen of the cases had severe suppurative adenitis and, in some, there was necrosis of the Palate.

And 22 of them had Otitis.

No injurious effect of Urotropine was noticed, though it was tried in some of the cases for 21 days in succession.

He also notes the case of a patient who was admitted with Nephritis on the 7th day of the disease. Urotropine was given for two days and the albuminuria disappeared and did not recur.
I started the administration of Urotropine in one case, a boy of 7, in the middle of the Nephritis. He was admitted to Hospital on the 10th. July 1905 and his temperature rose that evening to 103 °F. On July 25th., the 19th. day of the disease, he developed albuminuria and oedema of the face and ankles and passed only 12 ounces of urine with renal casts, but no blood.

The albuminuria diminished and on July the 29th. there was only a trace of albumin, but that evening he developed sharp uraemic convulsions and required to be bled and have chloroform administered.

He did very well, and by August 1st. his urine was clear, and the amount 28 ounces.

But on August the 5th. Haematuria and Albuminuria appeared and continued to be present on August the 8th. when Urotropine was given in 5 grain doses, thrice daily.

On August the 11th, 12th, 13th, 14th, and 15th there were diminishing traces of blood and albumin and on August the 16th. the urine was clear, after 7 days treatment with Urotrophine, and remained so on
the patient's discharge from Hospital.

In this case then, where the kidneys were already acutely inflamed, the drug allayed the irritation rather than increased it.

Patschkowski finally refers to the case of a child who had received Urotropine and died on the 12th day.

The autopsy showed Endocarditis, Pericarditis, Pleurisy, a purulent and also a fresh splenic infarct and Peritonitis.

In this case the urine had remained free from albumin and the kidneys were found to be normal.

In a synopsis of Waterf's (1) article, the original of which appeared in the Roumanian language, it is stated that he thoroughly agrees with Widowitz in his favourable opinion of Urotropine as a prophylactic against Scariatinal Nephritis.

Posner (1) also remarks on the importance of urotropine as a prophylactic against catheter infection, Typhoid and Scarletinal Nephritis.

Heubner states that of 358 Scarletina patients seen by him in private practice, he saw only 10 Nephritis cases.

But he says most of these were mild cases, and he is of opinion that patients in private practice are better able to resist the attacks because of better nourishment.

During 4 years practice at the Berlin Charite Hospital 18.6 per cent of 383 cases had Nephritis.

In the Charlottenburg Municipal Hospital during the 2 years previous to the use of Urotropine, 37 out of 177 cases, i.e. 20.9 per cent were complicated with Nephritis.

Whereas there is now only 3.8 per cent with Nephritis, after the use of Urotropine as a prophylactic.

My experience with Urotropine, Hexamethylenetetramine and Metramine in the treatment of Scarletinal Nephritis.

In August 1905 I commenced to administer Urotropine to unselected cases of Scarletina and continued uninterruptedly till January 5th. 1906, by which time I was enabled to make notes on 300 cases which were admitted to Hospital in the early stages of the disease.

Apart from some cases sent in as Scarletina and which turned out to be something else, there are 20 cases which I did not count, being these sent into Hospital late on in the disease, when desquamation was well advanced, and also a few very mild doubtful cases.

Therefore, I think that by taking these precautions, I have given the drugs a much fairer test than by starting one patient, say, on the 3rd. day of the disease and another on the 18th. day, and then attempting to compare them.

In giving the drugs from the very commencement of
the disease, and looking upon them as urinary antiseptics. I was guided by the axiom that prevention is better than cure, and with the idea of aiding the kidney in combating the attacking virus.

The urine in all my cases was collected between 2 a.m. and 6 a.m., a fact which should be borne in mind as practically eliminating the possibility of Postural Albuminuria.

It was tested between 12 noon and 1 p.m. the same day.

The urine glasses were thoroughly cleansed before receiving the urine, and every possible care was taken to prevent contamination.

The two tests I relied on for the detection of albuminuria were:

1. Heller's test. Pour about \( \frac{1}{4} \) of an inch of pure nitric acid into a test-tube and then allow some of the urine gently to flow on its surface.
or pour about 2 inches of urine into the test-tube, slightly invert the tube and gently pour pure nitric acid down the side of the tube, a drop bottle is best.

If after standing for a minute or so no opaque white ring appeared at the junction of the two fluids, I regarded the urine as free from albumin.

As this test is capable of revealing .002 per cent albumin, it is certainly delicate enough for requirements of any practical clinical value.

2. If I was in any doubt; in addition, I boiled

1 inch or so of urine in a test-tube.

If it remained clear, when the reaction was still acid, I concluded that no albumin was present.

Turbidity on boiling is due to either albumin or earthy phosphates, the latter immediately disappear on the addition of a drop of pure nitric acid.
Mucin very occasionally causes a diffuse haze at the upper part of the fluid and the ring formed by Albumoses disappears on heating.

But being Fever urines the two things I found most likely to cause a mistake were acid Urates and Nitrate of Urea, but there was no difficulty in eliminating these, as the precipitate disappears on heating.

The following case is, I think worth mentioning, as the examination of the urine cleared up the diagnosis of the case.

A youth of 19 was sent in as a case of Scarlatina, but as the rash, tongue and Fauces did not look like it, he was isolated.

On the addition of Nitric acid to the urine I found a whitish cloud diffused through the urine, but no ring.

He had been treating himself for Gonorrhoea, and later, on obtaining and examining the medicine, I found that it contained Copaiba.
Heller's test is, I think, the most satisfactory, and when in doubt, if one carries out the boiling test in addition, there is little room for error.

It has been the custom in the City Hospital to consider one a case of Albuminuria which lasted more than 2 days, and I have adhered to this in my cases and statistics.

Those urines which I considered to be indicative of Nephritis, contained (1) blood along with albumin, or (2) Renal casts and albumin, or (3) Cases in which Uraemic convulsions appeared along with albuminuria.

But cases of albuminuria alone were not considered to be Nephritis, when there were no other clinical signs accompanying it indicative of renal inflammation.

Haematuria. For the detection of blood in the urine I relied upon the Guiac test and the microscope.
Urotropine.

Urotropine was given in 47 consecutive cases of early Scarlatina, irrespective of the case being mild or severe, from August 9th, 1905 to September 18th. And it was continued for 28 days; for if the Nephritis did not occur in that time, there was little likelihood of its occurring later.

The usual dose of 5 grains, thrice daily was given and proved to be not too much for children and at the same time determined the efficacy of small doses for adults.

In this series, NO CASE OF NEPHRITIS appeared, and only one with albuminuria made its appearance.

Only one case in this series missed getting Urotropine and that was an epileptic idiot who was suffering, in addition, from Phthisis, and who died within 4 days of admission.
Hexamethylenetetramine.

Hexamethylenetetramine was given in exactly the same manner as Urotropine with this exception, that I kept every third case, as it was admitted, as a control case and which was treated without drugs. This procedure was continued from September 18th to December 14th, with the result that out of 137 cases, 15 had Nephritis and 7 had Albuminuria. Of the 66 control cases, 6 contracted Nephritis and 1 had albuminuria.

A period with no drugs.

From December 14th to Dec. 27th. I administered no drugs to any of the fresh patients. Those who had not completed their 28 days with Hexamethylenetetramine were of course continued on it till the allotted time was up, just as some of the Urotropine cases overlapped those on Hexamethylenetetramine.
During this no drug period, out of 24 consecutive cases, 2 had Nephritis and one developed Albuminuria.

Metramine.

Metramine was given from December 27th, 1905 to January 5th, 1906.

26 Consecutive cases were treated with it and out of these 3 developed Nephritis and one had albuminuria.

Total of Cases.

Cases on Urotropine 47
" Hexamethylenetetramine 137
Control cases 66
Cases with no drugs 24
Cases on Metramine 26

Total 300
<table>
<thead>
<tr>
<th></th>
<th>8.8</th>
<th>7</th>
<th>8</th>
<th>90</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3.8</td>
<td>1</td>
<td>3</td>
<td>26</td>
<td>Initial case</td>
</tr>
<tr>
<td></td>
<td>4.1</td>
<td>1</td>
<td>2</td>
<td>24</td>
<td>No drug case</td>
</tr>
<tr>
<td></td>
<td>0.8</td>
<td>1</td>
<td>6</td>
<td>66</td>
<td>Control case</td>
</tr>
<tr>
<td></td>
<td>1.5</td>
<td>1</td>
<td>15</td>
<td>137</td>
<td>Combination</td>
</tr>
<tr>
<td></td>
<td>0.9</td>
<td>7</td>
<td>15</td>
<td>47</td>
<td>Combination</td>
</tr>
</tbody>
</table>
|    | 2.3 | 0  | 1  | 0  | Surgery, etc.

|    | 3.8 | 1  | 3  | 26 | Initial case |
|    | 4.1 | 1  | 2  | 24 | No drug case |
|    | 0.8 | 1  | 6  | 66 | Control case |
|    | 1.5 | 1  | 15 | 137| Combination |
|    | 0.9 | 7  | 15 | 47 | Combination |
|    | 2.3 | 0  | 1  | 0  | Surgery, etc.

**Table I.** Number and percentage of albuminuria cases with nephritis and percentage of number of cases of albuminuria with nephritis according to each method of treatment.
From the above table it will be seen that Urotropine comes out of the ordeal very creditably.

It may be urged with justice that from August 9th. to September 18th. is a time when there is usually very little Scarlatinal Nephritis.

As compared with other years; for the same period in 1904 in the City Hospital, there were 3 Nephritis and 5 albuminuria cases.

And for the same period in 1903 there were 3 Nephritis and 5 albuminuria cases.

Hexamethylenetetramine had the longest test, and with its 10.9 per cent with Nephritis it is distinctly above the Nephritis percentage for 1905, which is 5.9 per cent.

But this drug was administered from September 18th. to December 14th., a period when most of the Nephritis cases appear, as is well seen in Tables 3, 4 and 5.

The Control Cases to Hexamethylenetetramine, which, of course, were treated with no drugs, and those that I have classified as "no drug cases", for the convenience of reference,
with their 8.8 per cent of Nephritis give a fair idea of the increase of Nephritis in the late Autumn, but still they are 2.1 per cent below that of the Hexamethylenetetramine cases.

Hexamethylenetetramine with its 3 Nephritis cases out of a total of 26 has a percentage of 11.5, which is higher than any of the others, but as a matter of fact it has only one more Nephritis case against it than the comparable 24 "No drug" cases from Dec. 14th to Dec. 27th.

So that comparing Hexamethylenetetramine with its Control Cases; and Metramine with the "no drug" cases immediately preceding it, we see that there is very little to choose between these 2 drugs, and although they have certainly not diminished the Nephritis percentage, yet they have not raised it to any marked degree.

The Nephritis with Hexamethylenetetramine is 1.1 per cent above its control cases.

The Nephritis with Metramine is 3.2 per cent above its comparable cases.
Prices of the drugs.

The prices of these show a wide difference.
And as one would expect, the proprietary drugs are twice and three times as much as the commercial article.
The following, which I ascertained from the proprietors, represents the prices of the drugs in the powdered form. The tabloid form is more expensive and is not necessary, as the drugs are all pleasant to take.

- Hexamethylenetetramine 8d. per ounce.
- Metramine 1/6d per ounce.
- Urotropine 2/9d per ounce.

From the following table (2) it will be seen that there has been a yearly alteration in the Nephritis percentage.
The large number of cases in 1903 was due to a milk infection in February.
A milk-maid, who had suffered from Scarlatina and was desquamating, had been milking the cows, and an epidemic was started amongst those persons supplied with milk from that particular dairy.
<table>
<thead>
<tr>
<th>Year</th>
<th>6.67</th>
<th>4.35</th>
<th>2.96</th>
<th>1.93</th>
<th>4.436</th>
<th>52.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>1903</td>
<td>7.2</td>
<td>5.9</td>
<td>52</td>
<td>43</td>
<td>117</td>
<td>&quot;</td>
</tr>
<tr>
<td>1904</td>
<td>12.8</td>
<td>3.3</td>
<td>110</td>
<td>69</td>
<td>8.59</td>
<td>&quot;</td>
</tr>
<tr>
<td>1905</td>
<td>5.7</td>
<td>3.3</td>
<td>67</td>
<td>62</td>
<td>115.7</td>
<td>&quot;</td>
</tr>
<tr>
<td>1906</td>
<td>3.8</td>
<td>2.9</td>
<td>21</td>
<td>117</td>
<td>519</td>
<td>&quot;</td>
</tr>
<tr>
<td>1907</td>
<td>3.7</td>
<td>2.2</td>
<td>26</td>
<td>28</td>
<td>537</td>
<td>&quot;</td>
</tr>
<tr>
<td>1908</td>
<td>4.4</td>
<td>2.3</td>
<td>26</td>
<td>14</td>
<td>587</td>
<td>&quot;</td>
</tr>
</tbody>
</table>

Table 2. Comparison of Rabies cases from 1900 to 1906.
Table 3. Monthly Comparison of Nephritis.

For the year 1903.

<table>
<thead>
<tr>
<th>Month</th>
<th>Number of Cases</th>
<th>Nephritis Cases</th>
<th>Nephritis percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>January</td>
<td>70</td>
<td>2</td>
<td>2.8</td>
</tr>
<tr>
<td>February</td>
<td>108</td>
<td>9</td>
<td>8.3</td>
</tr>
<tr>
<td>March</td>
<td>128</td>
<td>6</td>
<td>4.6</td>
</tr>
<tr>
<td>April</td>
<td>70</td>
<td>7</td>
<td>10.0</td>
</tr>
<tr>
<td>May</td>
<td>78</td>
<td>5</td>
<td>6.4</td>
</tr>
<tr>
<td>June</td>
<td>63</td>
<td>3</td>
<td>4.7</td>
</tr>
<tr>
<td>July</td>
<td>73</td>
<td>5</td>
<td>6.5</td>
</tr>
<tr>
<td>August</td>
<td>103</td>
<td>5</td>
<td>4.8</td>
</tr>
<tr>
<td>September</td>
<td>124</td>
<td>4</td>
<td>3.2</td>
</tr>
<tr>
<td>October</td>
<td>136</td>
<td>5</td>
<td>3.6</td>
</tr>
<tr>
<td>November</td>
<td>112</td>
<td>7</td>
<td>6.2</td>
</tr>
<tr>
<td>December</td>
<td>89</td>
<td>4</td>
<td>4.4</td>
</tr>
<tr>
<td>For the whole year</td>
<td>1157</td>
<td>62</td>
<td>5.3</td>
</tr>
</tbody>
</table>
Table 4. Monthly Comparison of Nephritis

For the year 1904.

<table>
<thead>
<tr>
<th>Month</th>
<th>Number of Cases</th>
<th>Nephritis Cases</th>
<th>Nephritis percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>January</td>
<td>90</td>
<td>1</td>
<td>1.1</td>
</tr>
<tr>
<td>February</td>
<td>84</td>
<td>4</td>
<td>4.7</td>
</tr>
<tr>
<td>March</td>
<td>87</td>
<td>3</td>
<td>3.4</td>
</tr>
<tr>
<td>April</td>
<td>52</td>
<td>4</td>
<td>7.6</td>
</tr>
<tr>
<td>May</td>
<td>51</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>June</td>
<td>62</td>
<td>3</td>
<td>4.8</td>
</tr>
<tr>
<td>July</td>
<td>53</td>
<td>2</td>
<td>3.7</td>
</tr>
<tr>
<td>August</td>
<td>51</td>
<td>1</td>
<td>1.9</td>
</tr>
<tr>
<td>September</td>
<td>70</td>
<td>2</td>
<td>2.8</td>
</tr>
<tr>
<td>October</td>
<td>106</td>
<td>4</td>
<td>3.8</td>
</tr>
<tr>
<td>November</td>
<td>86</td>
<td>3</td>
<td>3.1</td>
</tr>
<tr>
<td>December</td>
<td>67</td>
<td>2</td>
<td>2.9</td>
</tr>
<tr>
<td>For the whole year</td>
<td>859</td>
<td>29</td>
<td>3.3</td>
</tr>
</tbody>
</table>
Table 5: Monthly comparison of nephritis

For the year 1905.

<table>
<thead>
<tr>
<th>Month</th>
<th>Number of cases</th>
<th>Nephritis cases</th>
<th>Nephritis percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>January</td>
<td>58</td>
<td>2</td>
<td>3.4</td>
</tr>
<tr>
<td>February</td>
<td>61</td>
<td>2</td>
<td>3.2</td>
</tr>
<tr>
<td>March</td>
<td>55</td>
<td>3</td>
<td>5.4</td>
</tr>
<tr>
<td>April</td>
<td>56</td>
<td>3</td>
<td>5.3</td>
</tr>
<tr>
<td>May</td>
<td>45</td>
<td>3</td>
<td>6.6</td>
</tr>
<tr>
<td>June</td>
<td>33</td>
<td>1</td>
<td>2.8</td>
</tr>
<tr>
<td>July</td>
<td>47</td>
<td>1</td>
<td>2.1</td>
</tr>
<tr>
<td>August</td>
<td>52</td>
<td>1</td>
<td>1.7</td>
</tr>
<tr>
<td>September</td>
<td>72</td>
<td>4</td>
<td>5.5</td>
</tr>
<tr>
<td>October</td>
<td>84</td>
<td>10</td>
<td>11.9</td>
</tr>
<tr>
<td>November</td>
<td>79</td>
<td>7</td>
<td>8.8</td>
</tr>
<tr>
<td>December</td>
<td>75</td>
<td>6</td>
<td>8.0</td>
</tr>
<tr>
<td>For the whole year</td>
<td>717</td>
<td>43</td>
<td>5.9</td>
</tr>
</tbody>
</table>
Table 6. Age distribution of nephritis for the year 1903.

<table>
<thead>
<tr>
<th>Years of Age</th>
<th>Cases of Nephritis</th>
<th>Years of Age</th>
<th>Cases of Nephritis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>17</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>18</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>7</td>
<td>19</td>
<td>1</td>
</tr>
<tr>
<td>4</td>
<td>6</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>10</td>
<td>21</td>
<td>1</td>
</tr>
<tr>
<td>6</td>
<td>11</td>
<td>22</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>8</td>
<td>23</td>
<td>1</td>
</tr>
<tr>
<td>8</td>
<td>1</td>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>3</td>
<td>25</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>2</td>
<td>26</td>
<td>0</td>
</tr>
<tr>
<td>11</td>
<td>0</td>
<td>27</td>
<td>1</td>
</tr>
<tr>
<td>12</td>
<td>0</td>
<td>28</td>
<td>0</td>
</tr>
<tr>
<td>13</td>
<td>1</td>
<td>29</td>
<td>0</td>
</tr>
<tr>
<td>14</td>
<td>2</td>
<td>30</td>
<td>1</td>
</tr>
<tr>
<td>15</td>
<td>2</td>
<td>31</td>
<td>1</td>
</tr>
<tr>
<td>16</td>
<td>0</td>
<td>32</td>
<td>0</td>
</tr>
</tbody>
</table>

43 cases of nephritis out of the 62 for the year, i.e. 69.3% percent of the nephritis cases, occurred between the ages of 3 and 8 years. The case that occurred at the age of 1 year was fatal.
Table 7. AGE distribution of nephritis

For the year 1904.

<table>
<thead>
<tr>
<th>Years of Age</th>
<th>Cases of Nephritis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>2</td>
</tr>
<tr>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>15</td>
<td>1</td>
</tr>
</tbody>
</table>

26 cases of nephritis out of the 29 for the year i.e. 89.6 percent of the nephritis cases, occurred between the ages of 3 and 8 years.
Table 8. AGE distribution of nephritis for the year 1905.

<table>
<thead>
<tr>
<th>Years of Age</th>
<th>Cases of Nephritis</th>
<th>Years of Age</th>
<th>Cases of Nephritis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>12</td>
<td>5</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>14</td>
<td>1</td>
</tr>
<tr>
<td>4</td>
<td>5</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>5</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>5</td>
<td>17</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>7</td>
<td>18</td>
<td>1</td>
</tr>
<tr>
<td>8</td>
<td>3</td>
<td>19</td>
<td>1</td>
</tr>
<tr>
<td>9</td>
<td>1</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>2</td>
<td>21</td>
<td>1</td>
</tr>
<tr>
<td>11</td>
<td>2</td>
<td>22</td>
<td>0</td>
</tr>
</tbody>
</table>

28 cases of Nephritis out of the 43 for the year, i.e. 65.1 percent of the Nephritis cases, occurred between the ages of 3 and 8 years.
Table 9. Day of Onset of Nephritis

For the year 1903.

<table>
<thead>
<tr>
<th>Day of Disease</th>
<th>Cases of Nephritis</th>
<th>Day of Disease</th>
<th>Cases of Nephritis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st</td>
<td>0</td>
<td>22nd</td>
<td>8</td>
</tr>
<tr>
<td>2nd</td>
<td>0</td>
<td>23rd</td>
<td>6</td>
</tr>
<tr>
<td>3rd</td>
<td>1</td>
<td>24th</td>
<td>4</td>
</tr>
<tr>
<td>4th</td>
<td>0</td>
<td>25th</td>
<td>4</td>
</tr>
<tr>
<td>5th</td>
<td>1</td>
<td>26th</td>
<td>3</td>
</tr>
<tr>
<td>6th</td>
<td>0</td>
<td>27th</td>
<td>2</td>
</tr>
<tr>
<td>7th</td>
<td>1</td>
<td>28th</td>
<td>1</td>
</tr>
<tr>
<td>8th</td>
<td>0</td>
<td>29th</td>
<td>1</td>
</tr>
<tr>
<td>9th</td>
<td>0</td>
<td>30th</td>
<td>3</td>
</tr>
<tr>
<td>10th</td>
<td>0</td>
<td>31st</td>
<td>0</td>
</tr>
<tr>
<td>11th</td>
<td>1</td>
<td>32nd</td>
<td>1</td>
</tr>
<tr>
<td>12th</td>
<td>0</td>
<td>33rd</td>
<td>0</td>
</tr>
<tr>
<td>13th</td>
<td>0</td>
<td>34th</td>
<td>0</td>
</tr>
<tr>
<td>14th</td>
<td>0</td>
<td>35th</td>
<td>0</td>
</tr>
<tr>
<td>15th</td>
<td>2</td>
<td>36th</td>
<td>1</td>
</tr>
<tr>
<td>16th</td>
<td>1</td>
<td>37th</td>
<td>1</td>
</tr>
<tr>
<td>17th</td>
<td>0</td>
<td>38th</td>
<td>0</td>
</tr>
<tr>
<td>18th</td>
<td>2</td>
<td>39th</td>
<td>0</td>
</tr>
<tr>
<td>19th</td>
<td>2</td>
<td>40th</td>
<td>1</td>
</tr>
<tr>
<td>20th</td>
<td>5</td>
<td>41st</td>
<td>1</td>
</tr>
<tr>
<td>21st</td>
<td>9</td>
<td>42nd</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>50th</td>
</tr>
</tbody>
</table>
Table 10. **Day of Onset of nephritis**

For the year 1904.

<table>
<thead>
<tr>
<th>Day of Disease</th>
<th>Cases of Nephritis</th>
<th>Day of Disease</th>
<th>Cases of Nephritis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st</td>
<td>0</td>
<td>19th</td>
<td>0</td>
</tr>
<tr>
<td>2nd</td>
<td>0</td>
<td>20th</td>
<td>0</td>
</tr>
<tr>
<td>3rd</td>
<td>1</td>
<td>21st</td>
<td>2</td>
</tr>
<tr>
<td>4th</td>
<td>1</td>
<td>22nd</td>
<td>3</td>
</tr>
<tr>
<td>5th</td>
<td>0</td>
<td>23rd</td>
<td>3</td>
</tr>
<tr>
<td>6th</td>
<td>0</td>
<td>24th</td>
<td>4</td>
</tr>
<tr>
<td>7th</td>
<td>0</td>
<td>25th</td>
<td>0</td>
</tr>
<tr>
<td>8th</td>
<td>1</td>
<td>26th</td>
<td>2</td>
</tr>
<tr>
<td>9th</td>
<td>0</td>
<td>27th</td>
<td>1</td>
</tr>
<tr>
<td>10th</td>
<td>0</td>
<td>28th</td>
<td>0</td>
</tr>
<tr>
<td>11th</td>
<td>0</td>
<td>29th</td>
<td>1</td>
</tr>
<tr>
<td>12th</td>
<td>0</td>
<td>30th</td>
<td>1</td>
</tr>
<tr>
<td>13th</td>
<td>0</td>
<td>31st</td>
<td>1</td>
</tr>
<tr>
<td>14th</td>
<td>0</td>
<td>32nd</td>
<td>0</td>
</tr>
<tr>
<td>15th</td>
<td>0</td>
<td>33rd</td>
<td>0</td>
</tr>
<tr>
<td>16th</td>
<td>2</td>
<td>34th</td>
<td>1</td>
</tr>
<tr>
<td>17th</td>
<td>0</td>
<td>35th</td>
<td>1</td>
</tr>
<tr>
<td>18th</td>
<td>2</td>
<td>48th</td>
<td>1</td>
</tr>
</tbody>
</table>
Table II. Day of ONSET of nephritis

For the year 1905.

<table>
<thead>
<tr>
<th>Day of Disease</th>
<th>Cases of nephritis</th>
<th>Day of Disease</th>
<th>Cases of nephritis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1\textsuperscript{st}</td>
<td>0</td>
<td>24\textsuperscript{st}</td>
<td>2</td>
</tr>
<tr>
<td>2\textsuperscript{nd}</td>
<td>2</td>
<td>25\textsuperscript{st}</td>
<td>0</td>
</tr>
<tr>
<td>3\textsuperscript{rd}</td>
<td>2</td>
<td>26\textsuperscript{st}</td>
<td>2</td>
</tr>
<tr>
<td>5\textsuperscript{th}</td>
<td>0</td>
<td>27\textsuperscript{st}</td>
<td>0</td>
</tr>
<tr>
<td>12\textsuperscript{th}</td>
<td>1</td>
<td>28\textsuperscript{st}</td>
<td>1</td>
</tr>
<tr>
<td>13\textsuperscript{th}</td>
<td>1</td>
<td>29\textsuperscript{st}</td>
<td>2</td>
</tr>
<tr>
<td>14\textsuperscript{th}</td>
<td>1</td>
<td>30\textsuperscript{st}</td>
<td>3</td>
</tr>
<tr>
<td>15\textsuperscript{th}</td>
<td>0</td>
<td>31\textsuperscript{st}</td>
<td>0</td>
</tr>
<tr>
<td>16\textsuperscript{th}</td>
<td>4</td>
<td>36\textsuperscript{th}</td>
<td></td>
</tr>
<tr>
<td>17\textsuperscript{th}</td>
<td>1</td>
<td>37\textsuperscript{st}</td>
<td>1</td>
</tr>
<tr>
<td>18\textsuperscript{th}</td>
<td>0</td>
<td>38\textsuperscript{st}</td>
<td>0</td>
</tr>
<tr>
<td>19\textsuperscript{th}</td>
<td>1</td>
<td>39\textsuperscript{st}</td>
<td>0</td>
</tr>
<tr>
<td>20\textsuperscript{th}</td>
<td>4</td>
<td>40\textsuperscript{st}</td>
<td>1</td>
</tr>
<tr>
<td>21\textsuperscript{st}</td>
<td>6</td>
<td>41\textsuperscript{st}</td>
<td>1</td>
</tr>
<tr>
<td>22\textsuperscript{nd}</td>
<td>3</td>
<td>42\textsuperscript{st}</td>
<td>1</td>
</tr>
<tr>
<td>23\textsuperscript{rd}</td>
<td>5</td>
<td>43\textsuperscript{st}</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>60\textsuperscript{st}</td>
<td>1</td>
</tr>
</tbody>
</table>
Table 12. Comparison of ONSET of Nephritis of the Hexamethylenetetramine cases and those in the year 1905 that received NO prophylactic drug treatment against nephritis.

<table>
<thead>
<tr>
<th>HEXAMETHYLENETETRAMINE CASES</th>
<th>NO DRUG CASES OF THE YEAR 1905</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DAY OF DISEASE</strong></td>
<td><strong>CASES OF NEPHRITIS</strong></td>
</tr>
<tr>
<td>1st</td>
<td>0</td>
</tr>
<tr>
<td>to 10</td>
<td></td>
</tr>
<tr>
<td>12th</td>
<td>1</td>
</tr>
<tr>
<td>13th</td>
<td>1</td>
</tr>
<tr>
<td>14th</td>
<td>0</td>
</tr>
<tr>
<td>15th</td>
<td>0</td>
</tr>
<tr>
<td>16th</td>
<td>3</td>
</tr>
<tr>
<td>17th</td>
<td>1</td>
</tr>
<tr>
<td>18th</td>
<td>0</td>
</tr>
<tr>
<td>19th</td>
<td>1</td>
</tr>
<tr>
<td>20th</td>
<td>1</td>
</tr>
<tr>
<td>21st</td>
<td>2</td>
</tr>
<tr>
<td>22nd</td>
<td>0</td>
</tr>
<tr>
<td>23rd</td>
<td>5</td>
</tr>
<tr>
<td>24th</td>
<td>1</td>
</tr>
<tr>
<td>25th</td>
<td>0</td>
</tr>
<tr>
<td>to 60th</td>
<td></td>
</tr>
</tbody>
</table>
Table 13. AGE distribution, day of ONSET and TIME TAKEN for the urine to clear up in the nephritis cases of the patients to whom METRAMINE was administered.

<table>
<thead>
<tr>
<th>Age</th>
<th>Day of Disease</th>
<th>Nephritis cases</th>
<th>Time taken for urine to clear up</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 years</td>
<td>26th</td>
<td>1</td>
<td>7 days</td>
</tr>
<tr>
<td>19 &quot;</td>
<td>2nd</td>
<td>1</td>
<td>6 &quot;</td>
</tr>
<tr>
<td>21 &quot;</td>
<td>29th</td>
<td>1</td>
<td>19 &quot;</td>
</tr>
</tbody>
</table>

I also made tables out for the length of time taken before the urine was clear of blood and albumin in the nephritis and Albinuriae cases for 1903, 1904 and 1905. But as so many of them cleared up in about 10 days, and after a lapse of about 14 days, Albinuriae reappeared for a period of 7 days or so, I did not consider them of sufficient interest for inclusion in extenso. It was usually about 23 days before the urine was clear of albumin. Of course, some of the urines cleared up in as short a time as 3 days, whilst others were not free of albumin, at one time or another, for as long as 60 days.
Table 14. Comparison of the time taken for the urine to clear up in the hexamethylenetetramine cases and those cases in the year 1905 that received no prophylactic drug treatment.

<table>
<thead>
<tr>
<th>Cases with Hexamethylenetetramine</th>
<th>No Drug Cases of the Year 1905</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days taken for urine to clear up</td>
<td>Nephritis cases</td>
</tr>
<tr>
<td>-----------------------------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>2</td>
</tr>
<tr>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>11</td>
<td>2</td>
</tr>
<tr>
<td>12</td>
<td>1</td>
</tr>
<tr>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>
The Hexamethylenetetramine cases, it will be seen, from Table 14, did not clear up any quicker, nor did they, on the other hand, last any longer, than the cases with no drugs.

Table 14, however, cannot illustrate the fact that the Hexamethylenetetramine cases were, on the whole, slighter cases of nephritis than those with no drugs, which I found to be the case.

One case, however, a boy of 8 years, developed Uraemic convulsions on the 22nd day of the disease with premonitory symptoms for only 3 hours. There was no Albuminuria before the attack, and after the Uraemia was over, the urine became quite albumin-free in 6 days, and the boy made a good recovery.

I should, perhaps, say that none of my 300 cases ended fatally.

---

**Table 15. The present statistics of the prophylactic treatment of Scarletinal nephritis with UROTROPINE.**

<table>
<thead>
<tr>
<th></th>
<th>CASES</th>
<th>NEPHRITIS</th>
<th>NEPHRITIS PERCENTAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Widowski</td>
<td>102</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Patschkowski</td>
<td>52</td>
<td>2</td>
<td>3.8%</td>
</tr>
<tr>
<td>Buttersack</td>
<td>35</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>H. P. Thompson</td>
<td>47</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
Conclusions.

1. Scarlatinal Nephritis is a distinct part of the disease, and should not be looked upon as an inevitable sequela, which presents itself in a certain percentage of cases; and as such it should be open to treatment.

2. The cause of Scarlatina is an organism, but of what particular variety, sufficient evidence has not been given to determine it.

3. The only form of treatment that is likely to be of any real value in countering the Nephritis, is the prophylactic; the object being to either kill outright or to weaken the virus by a substance, which is in itself harmless.

And as the virus is in the general circulation at the beginning of the disease, it must perforce be present in the kidneys and urinary system in general.
4. The diet and general medical supervision of the patient should be strict.
A milk and farinaceous diet should be insisted upon for the first 3 weeks, during which time patients should be kept in bed, and they should be kept in the house for the 2 weeks following. And care should be taken until desquamation is completed.
Patients should be encouraged to take plenty of diluents, as long as there is no evidence of fluid collecting in any part of the body.

5. All methods of excretion should be encouraged and helped in every way possible.
Thus the Fauces should be frequently swabbed, gently, and gargled with Sodium Bicarbonate solution to remove the mucus, and this should be followed by a weak antiseptic solution, e.g., Chlorine water or Listerine.
A Higginson's syringe should be used when gargling is not feasible, but care should be taken that it is not done too forcibly, to cause the extremely infectious Tonsillary exudate to be driven up the Eustachian tubes, as the child splutters and swallows.

Desquamation should be encouraged by frequent sponging and occasional tepid baths, to prevent a clogging of the exits of the sebaceous glands with partially cast off epithelium.

Constipation should, of course, be avoided, but purging lowers the arterial tension and should be guarded against.

For, a low arterial tension is detrimental to diuresis, which should be encouraged.

Rather above than below the normal amount of urine should be the guide.

The daily examination of the urine should be a matter of routine.

6. With regard to the use of a prophylactic drug against the Nephritis of Scarlatina, the only one
that has proved itself to be of any value, in my experience, is Urotropine.

Hexamethylenetetramine certainly did not succeed in diminishing the Nephritis, nor did Metramine. If anything, the Nephritis was slightly increased by these two latter, if one compares the cases treated by them, and the ones treated with no drugs, in the same period.

It is true that Urotropine had the distinct advantage of having cases in August and the first 18 days of September, which is a time that the Nephritis percentage is usually low. But the fact, that of the 47 consecutive cases treated with Urotropine, not one had Nephritis, and only one had Albuminuria, is, I consider, encouraging enough to suggest the further use of the drug in Scarlatina.

Hexamethylenetetramine was substituted for Urotropine, in my cases, because it was so much cheaper in treating a large number of patients, but I do not
consider that it is the exact equivalent of Urotropine, when considered from the clinical results.

I see no reason to believe that Metramine is therapeutically any better or worse than Hexamethylene-tetramine.

7. And, therefore, finally, I would suggest that all cases of Scarlatina should be treated from the beginning with 5 grain doses, thrice daily, for children up to 12 years; and for patients above that age, 7½ grains, thrice daily.

In the administration of this drug the importance of dilution with water must not be overlooked.

And I would recommend that this treatment should be continued to the end of the 28th. day of the disease.
General Index.

A.
Administration of Urotropine, Hexamethylenetetramine and Métramime. 58.
Age: its influence on Scarlatinal nephritis 30, 31.
Albumin test 80 - 83.
Albuminuria, Early 4, 5,
      Late 5,
      Intermittent 10
Anthrax bacillus, 11.
Autumn: its influence in Scarlatinal nephritis 27.
Aminoform, 51

B
Baths, 40-43
Bacteriology 8-22
Bacillus Scarlatinae 13
Blood Examination 36
   " Serum of Convalescents 48.

C
Causation of Scarlatinal Nephritis 4-8
Chilling, 5, 23, 26.
Control Cases, 85, 88, 89.
Credé's Ointment, 44.
Conclusions as to Aetiology of Scarlatinal Nephritis 37
   " as to prophylactic treatment 105-9
Cystamin 51

D
Desquamation, 5, 23.
Dietetic albuminuria, 6
Diuretics, 49
Diaphoretics, 50
Diphtheroid bacilli, 15
Diplococcus Scarlatinae, 20
Dosage, 62.

E
Epithelium, Renal 5, 7.
Erysipelas & Scarlatina, 16
Eucalyptus Oil, 39
General Index

F
Fatigue albuminuria, 8
Febrile " 5
Formaldehyde, 54-7

G
Glomerulus, 11
Guiac reaction, 83.
Griserine, 52.

H
Haematuria, 83
Helmitol, 52
Hetralin, 52
Hexamethylenetetramine, 53
  " preparation of 55
  cases 60, 85, 89, 104.

I
Infarcts, organismal
  Embolic of Kidney 22
Infants, insusceptibility 30, 31.
Intermittent Albuminuria 10.
Inoculability of Scarlatina 8, 9.
Inoculation, Preventive 47

J
Japanese, immunity of 9,11
Jequirity bacillus, 11

K
Kidney, organismal embolic
  infarcts of, 22.

L
London, mortality 28

M
Micrococi, 10.
Meteorological influence 34, 35.
Metramine, 52
  " cases, 61, 86, 89.
  preparation of 55.
Monthly statistics 92, 93, 94.
Mona Scaldatosum, 10.
Mucin, 82.
General Index.

N

Nephritis, glomerular, 7
" Variation of
Int.ensity. 26.
New Urotropine. 52
"No drug cases" 85, 86.
Onset of Nephritis: 98, 99, 100.

O

P

Patients specially referred
to 23, 24, 46, 59, 60,
61, 76, 77, 82, 104.
Postural & Physiological
Albuminuria. 8, 80.
Pneumococci, 15, 18.
Prices of Drugs, 90.
Prophylaxis of Scarlatinal
Nephritis, 38-50.
Purgatives, 50.

R

Rainfall, influence of 36.
Race, influence of 9, 11.

S

Sex, influence of, 31.
Season: its relation to
Scarlatinal Nephritis, 27.
Social influence, 34, 78.

T

Streptococcus 11-19
" conglom.eratorus. 17
Schizomycetes, 7
Staphylococcus, 15, 18.
Serotherapy, 44-47

Tables 1 to 15, 87-104.
General Index.

T (continued)

Tilletia Scarlatinosa, 10
Type of Epidemic, 26, 28, 67.
Total of cases treated. 86.

U
Urine, collection of, 80.
" testing of 80-83.
Urinary Antiseptics. 51.
Uritone 51
Urotropine, preparation of, 54
" chemical & pharmacological properties 56
" cases, 60, 66-68, 72-77, 79, 84.
" animal experiments with, 61.

V
Ventilation 39
Virus of Scarlatina 7, 8, 33, 35.
" Seasonal influence on, 27.
# Reference Index

<table>
<thead>
<tr>
<th>A</th>
<th>D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ashmed, 9</td>
<td>Dopter, 18</td>
</tr>
<tr>
<td>Baginsky, 14, 19, 21, 44</td>
<td>D'Espine, 13, 14, 21</td>
</tr>
<tr>
<td>Bardt, 14</td>
<td>Edington, 13</td>
</tr>
<tr>
<td>Bartels, 25</td>
<td>Eimslitz, 4</td>
</tr>
<tr>
<td>Ballard, 35</td>
<td></td>
</tr>
<tr>
<td>Babes, 14, 17, 21</td>
<td></td>
</tr>
<tr>
<td>Bergé, 16</td>
<td></td>
</tr>
<tr>
<td>Bexançon, 18</td>
<td>Feltz, 10</td>
</tr>
<tr>
<td>Beyer, 53</td>
<td>Fehleisen, 18</td>
</tr>
<tr>
<td>Begbie, Dr. Warburton, 5</td>
<td>Fodor, 54</td>
</tr>
<tr>
<td>Birch-Hirschfeld, 10</td>
<td>Fraenkel, 14, 21</td>
</tr>
<tr>
<td>Besredka, 18</td>
<td>Freudenberg, 14</td>
</tr>
<tr>
<td>Biss, 61</td>
<td></td>
</tr>
<tr>
<td>Bouchard, 11</td>
<td>Gerhardt, 5</td>
</tr>
<tr>
<td>Bourges, 14</td>
<td>Gresswell, 5</td>
</tr>
<tr>
<td>Brewer, 58</td>
<td>Grawitz, 10</td>
</tr>
<tr>
<td>Buxbaum, 40</td>
<td></td>
</tr>
<tr>
<td>Butlerow, 53</td>
<td></td>
</tr>
<tr>
<td>Buttersack 72, 73, 104</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>B</th>
<th>E</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>C</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Casper, 58</td>
<td></td>
</tr>
<tr>
<td>Cohnheim, 7, 10</td>
<td></td>
</tr>
<tr>
<td>Class, 20, 21</td>
<td></td>
</tr>
<tr>
<td>Coze, 10</td>
<td></td>
</tr>
<tr>
<td>Crooke, 10, 14, 21</td>
<td></td>
</tr>
<tr>
<td>Crookshank, 12</td>
<td></td>
</tr>
<tr>
<td>Curganven, 39</td>
<td></td>
</tr>
</tbody>
</table>
Reference Index.

H
Hallier, 9
Heubner, 14, 18, 21, 63, 78.
Hirsch, 27
Hlava, 21.
Hoffmann, 54.

J
Jaccoud, 16, 38.
Jamieson, 13
Johannessen, 67.
Josias, 44.
Juhel-Renoy, 21.
Jürgensen, 42.

K
Ker, Claude B., 3
Klebs, 10, 11.
Klein, 11, 12, 21.
Klamann, 10
Kurth
Küster

L
Leroy, 8
Lenharz, 18
Lewis, 14
Letzerich, 11
Leichtenstein, 42
Löffler, 14, 18.
Lutten 6
Longstaff, 35.
Longhurst, 13.

de Marignac, 13, 14.
Marmorek, 21, 45.
Miguel, 8
Moschatos, 54.
Moser, 18, 21, 45.

N
Nicolaier, 51, 54, 55, 58, 62.
Patschkowski, 74, 77, 104.

Parry, 59.
Pearce, 18.
Power, 11
Posner, 78
Pohl Pinkus, 10
Priestley, 39.
Reference Index.

R
Raskin, 14, 18, 21.
Riess, 10
Registrar-General, 31.
Rosenbach, 17
Roger, 48.

S
Schill, 41.
Slawyk, 19, 21
Soerensen, 21
Sommerfeld, 21
Smith, Horton, 63
Stewart, Prof. Sir T.G.
Smith, 13
Steiner, 4
Stoll, 8
Stickler, 47.

T
Tanago, 58
Tollens, 54
Thomas, 4, 41.
Tschauer, 10.

V
Vierodt, 40.

W
Wateff, 77
Wassermann, 19.
Wyllie, Prof. John, 4.
Windell, 58.
Widal, 18.
Wurtz, 14.
Widowitz, 36, 65-67, 104.