https://theses.gla.ac.uk/

Theses Digitisation:

https://www.gla.ac.uk/myglasgow/research/enlighten/theses/digitisation/

This is a digitised version of the original print thesis.

Copyright and moral rights for this work are retained by the author

A copy can be downloaded for personal non-commercial research or study, without prior permission or charge

This work cannot be reproduced or quoted extensively from without first obtaining permission in writing from the author

The content must not be changed in any way or sold commercially in any format or medium without the formal permission of the author

When referring to this work, full bibliographic details including the author, title, awarding institution and date of the thesis must be given

Enlighten: Theses
https://theses.gla.ac.uk/
research-enlighten@glasgow.ac.uk

"URETHRITIS"

THESIS SUBMITTED FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

OF THE UNIVERSITY OF GLASGOW

BY

TADEUSZ, A.H PASIECZNY, M.D., (WARSAW).

ProQuest Number: 10656386

All rights reserved

INFORMATION TO ALL USERS
The quality of this reproduction is dependent upon the quality of the copy submitted.

In the unlikely event that the author did not send a complete manuscript
and there are missing pages, these will be noted. Also, if material had to be removed,
a note will indicate the deletion.

ProQuest 10656386

Published by ProQuest LLC (2017). Copyright of the Dissertation is held by the Author.

All rights reserved.
This work is protected against unauthorized copying under Title 17, United States Code
Microform Edition © ProQuest LLC.

ProQuest LLC.
789 East Eisenhower Parkway
P.O. Box 1346
Ann Arbor, MI 48106 – 1346

DECLARATION.

I declare that the Thesis submitted has been composed by myself.

The subject matter except pages: 32-35, 75-79, 95-104, and 116-119 represents original work.

T. Pasieczny

T. Pasieczny M.D.

5th July, 1957.

CONTENTS.

I. INTRODUCTION.

In the last ten years Non-Gonococcal Urethritis has started to increase rapidly in the statistics of all countries; the number of cases becoming second only to gonorrhoea in Britain, while in other countries the diseases are of equal incidence. In view of the prevalence of this serious disease, whose aetiology is incompletely understood, many venereologists and bacteriologists have tackled this problem throughout the world.

Having been interested in venereal diseases for many years, and having opportunities during the last war and especially since the end of 1948 to work regularly in the local venereal disease clinics I started in 1950 to collect material connected with all aspects of urethritis.

I decided to undertake a more detailed study of urethritis in males, and it was the disease "Non Specific Urethritis" or more especially "Abacterial Urethritis" which induced me to do this work.

Gonorrhoea has always been known in the Old World as its name of Greek origin "a flow of semen" indicates. The problem of Non-Gonococcal Urethritis, however, was first raised in 1897 by Guiard, who described 3 cases of aseptic urethritis. Barlow 1899, Waelsch 1901, Hecht 1927 and many others since then have confirmed the first observations made by Guiard.

Before the discovery of sulphonamide drugs and penicillin, the treatment of gonorrhoea presented many serious difficulties. In uncomplicated cases of the disease treatment lasted usually for several weeks or even months. In cases complicated by epididymitis or prostatitis,

treatment was very much prolonged. In complicated and uncomplicated cases of gonorrhoea - doctors always expected and hoped that sooner or later the disease would be cured. In the past, however, there was a grave degree of scepticism regarding the value or outcome of the treatment of Non-Gonococcal Urethritis. The measures taken were the same as for gonorrhoea, although it was known that the treatment of Non-Gonococcal Urethritis presented greater difficulties than that of gonorrhoea itself. Recurrences were to be expected even after prolonged treatment and it was difficult to judge a case as satisfactorily cured.

Several factors contributed to relegate the question of Non-Gonococcal Urethritis to the background:

Gonorrhoea was much more common and its consequences - strictures, prostatitis, infertility (post epididymitic) and arthritis more serious, while the treatment of gonorrhoea was more satisfactory.

Cases of Non-Gonococcal Urethritis were fewer and complications rarer than in Gonorrhoea.

Each war produces an increase in the venereal diseases - so it was during the 1939-45 war. The use of sulphonamides during the early years of the war greatly facilitated the treatment of gonorrhoea. Although sulphonamides were a step forward in the treatment of Non-Gonococcal Urethritis, the proper treatment of N.G.U. was rather neglected. Since the advent of penicillin the treatment of gonorrhoea, complicated or otherwise - does not present any difficulties. It is not a problem today. A few years after the war there was a decrease in venereal diseases - especially syphilis. The incidence of gonorrhoea in some countries also showed this decrease, while in others it remained at pre-war level. The incidence of Non-Gonococcal Urethritis, however, increased

and now approaches that of gonorrhoea, and so has become a world wide problem.

In the clinics of England and Wales in 1951, there were 10,794 cases of Non-Gonococcal Urethritis as compared with 14,975 male cases of gonorrhoea. According to the report of the Chief Medical Officer of the Ministry of Health, in 1952 new cases of Non-Gonococcal Urethritis in men attending public venereal disease clinics in England and Wales numbered 11,552, and new cases of gonnrrhoea in men numbered 15,510. The statistical figures from the other West-European countries and U.S.A. show similar numbers.

11. INCIDENCE OF URETHRITIS IN VENEREAL DISEASE CLINICS OF GLASGOW.

Many years ago a special numerical code for medical records was introduced into all Glasgow Venereal Disease Clinics. For example:

No. 1. Primary Syphilis — Dark Ground +ve; W.R. -ve

No. 2. Primary Syphilis — Dark Ground +ve; W.R. +ve

No. 8. Acute Gonorrhoea

No.11. Non-Specific Venereal Infections. (N.S.V.I.)

No.12. Diseases other than Venereal Infections.

By means of this code figures I have collected the figures for Gonorrhoea (GC..) and Non-Specific Venereal Infections (N.S.V.I.), occuring during the years 1950-1956 inclusive. These are shown in Table 1.

It is necessary, however, to analyse further the figures of the Non-Specific Venereal Infections, as it is wrong to think that these cases consist only of Non-Gonococcal Urethritis. Many of these cases are of non-venereal origin and include diseases of the skin and genital organs associated with primary and secondary urethritis.

In Table 2. I have sub-divided the 441 cases of N.S.V.I. occuring in 1950 at the Broomielaw Clinic into the actual conditions which were present at the time of examination.

Incidence of Gonorrhoea (GC.) and Non Specific Venereal Infections (N.S.V.I.) in Glasgow Clinics.

Table 1.

	Venereal Disease Clinic					
	Broomielaw		Black Street		Paisley Road	
	GC.	N.S.V.I.	GC.	N.S.V.I.	GC.	N.S.V.I.
1950	560	441	630	460	219	183
1951	506	328	593	481	178	97
1952	566	393	591	453	195	130
1953	633	374	671	464	223	139
1954	637	547	540	521	Clinic Closed.	
1955	560	398	468	351		
1956	631	389	596	411		

Diseases classified at Broomielaw Clinic under Code 11.. i.e. Non-Specific Venereal Infections (N.S.V.I).

Table 2.

Disease	No.
Bacterial Non G.C. infection	183
Abacterial Infection.	39
Balanitis	103
Venereal Warts	39
Venereal Erosions	10
Pediculosis Pubis	9
Phimosis and Paraphimosis	9
Scabies	7
Desquamative urethritis	5
Herpes Genitalis	5
Epididymitis	4
Test of cure	4
Strictures of urethra	3
Pityriasis Rosea	2
Prostatic Abscess	2
Psoriasis	2
Lichen Planus	2
Lichen Sclerosus et atrophicus	2
Reiter's Disease	2
Orchitis	1
Furunculosis	2
Varicocoelle	1
Cowperitis	1
Cystitis	1
Keratodermia Blenorrhagica	1
Buboes	
Total	441

Corrected figures for Non Specific Venereal Infections (N.S.V.I.).

Table 3.

	Venereal Disease Clinic											
	Broomielaw				Black Street				Paisley Road			
	Bacterial N.G.U.	Abacterial Urethritis	Balanitis	Miscell.	Bacterial N.G.U.	Abacterial Urethritis	Balanitis	Miscell.	Bacterial N.G.U.	Abacterial Urethritis	Balanitis	Miscell.
1950	183	39	103	116	155	108	125	72	66	40	36	41
1951	156	41	61	70	186	98	104	93	34	19	25	19
1952	169	74	73	77	160	108	107	78	47	29	31	23
1953	198	48	58	70	158	95	117	94	49	29	42	19
1954	207	72	170	98	121	95	121	185				
1955	150	48	97	103	99	78	73	101				
1956	132	101	119	37	163	98	117	33				
Total	1196	423	681	571	1042	680	764	656	196	117	134	102

It would seem from Table 2, that several of the diseases were wrongly coded as No.11 and should have been correctly coded as No.12 i.e., diseases other than venereal infections. Diseases such as Psoriasis, Lichen Planus and Pityriasis Rosea, were coded as No.11, because they were related to sexual intercourse by the patient, while correctly speaking they should have been classified as Code No.12 diseases.

It is necessary, therefore, to show separately for each year the corrected figures for Non Specific Venereal Infections, and I have done this in Table 3.

I have chosen 4 main groups as follows:

1. Bacterial Non-Gonococcal Urethritis (B.N.G.U.),
2. Abacterial Urethritis (A.U.),
3. Balanitis, and,
4. Miscellaneae.

The term Miscellaneae has been used to group the various diseases shown in Table 2 which in my opinion were wrongly classified under Code No.11.

Groups (1) and (2) form corrected figures for Bacterial Non-Gonococcal Urethritis and Abacterial Urethritis and, in Table 4 (overleaf) are expressed as a percentage of Gonorrhoea compared with the figures for Gonorrhoea for the year 1950 - 1956.

Corrected figures of Gonorrhoea compared with Abacterial and Bacterial Non-Gonococcal Urethritis expressed as a percentage for the year 1950-1956.

Table 4.

	Venereal Disease Clinic								
	Broomielaw			Black Street			Paisley Road		
	GC.	N.G.U.	% of N.G.U. to GC.	GC.	N.G.U.	% of N.G.U. to GC.	GC.	N.G.U.	% of N.G.U. to GC.
1950	560	222	39.6	630	263	41.9	219	106	48.4
1951	506	197	38.9	593	284	47.8	178	53	29.8
1952	566	243	42.9	591	268	45.3	195	76	38.9
1953	633	246	38.9	671	253	37.7	223	78	34.9
1954	637	310	48.7	540	216	40.9	-	-	-
1955	560	168	30.0	468	177	37.8	-	-	-
1956	631	233	36.9	596	261	43.9	-	-	-

It will be noticed the percentage of the former varies from 29.8% to 48.7% but never exceeds 50%. These (percentage) figures although interesting from a theoretical aspect may not be suitable from a practicable standpoint, as it is difficult to exclude "Balanitis" and "Miscellaneae" from the problem of urethritis, as these two groups may play some part directly or indirectly in the production of urethritis. I have, therefore, divided my work into four main parts:

PART I. Cases with balanitis and miscellaneae which directly and indirectly play a considerable role in the development of urethritis.

PART II. Gonorrhoea mixed with other organisms.

PART III. Bacterial Non-Gonococcal Urethritis (B.N.G.U.).

PART IV. Abacterial Urethritis. (A.U.).

The previous statistical data were obtained from the medical records of the Venereal Disease Clinics of Glasgow. For practical purposes, however, my work has been confined to the Broomielaw and Black Street Clinics, and in the following pages I will discuss and described only those cases, which were investigated and treated by me.

111. PART 1.

BALANITIS.

Balanitis is an infection of the surface epithelium of the glans and prepuce. It occurs oftenest in phimotic subjects, particularly those, who pay little attention to hygiene.

Sometimes balanitis may follow sexual intercourse, and can be presumed to be venereal in origin. It occurs also in gonorrhoea, but is rarely caused by the gonococcus itself. In the mildest form the surface of the glans and prepuce is red, rough, and granular, and often there is erosion of the epithelium in patches with actual ulceration in the worst cases. There is usually some oedema of the prepuce.

The number of patients with balanitis and urethritis is fairly large, and forms the majority of cases in Part 1, and they are, therefore, discussed in some detail in the following paragraphs. The other cases, which form the "Miscellaneae" are made up of small numbers of a great variety of diseases all connected with urethritis - (see Table 2), and so I am of the opinion that they would be best summarised under a separate heading. This has been done in Appendix.

It is well known, that even acute balanitis is rarely complicated by urethritis. One hundred and ninety-eight cases of balanitis have been investigated and treated. The majority of the cases were uncomplicated, and varied from a mild infection of the surface epithelium of the glans and prepuce to a red, rough granular appearance of the surface with erosions and ulcerations.

In 13 cases (6.6%) the balanitis was associated with urethritis. The age group of the patients was between 18 and 47 years. Five of them had gonorrhoea previously, and one had gonorrhoea and latent syphilis. The remainder denied any previous venereal disease. All of them had recent sexual intercourse, and the incubation period varied from 2 to 17 days. All of these cases had mucous or muco-purulent discharges; pain and burning on micturition was present in 5 cases and frequency of micturition in 8 cases. The urine was as a rule hazy or clear with threads in first glass, and clear in the secomd glass. Microscopical examination of slides (Gram stained) revealed normal balanitic flora, (various Gr. + ve cocci, B. Coli, Smegma bacilli, Spirochaetes). In all these cases, with even very mild erosions Dark Ground examination was performed daily for several days, Wassermann reactions were repeated on several occasions.

One of these 13 cases is rare and interesting and deserves a detailed description. An Indian sailor, aged 27, was seen in the V.D. clinic in August 1953 suffering from: balanitis erosiva circinata of two weeks duration. Last sexual intercourse was three weeks previous to the onset of the disease. The balanitis was associated with an urethral discharge, and there was also a lymphangitis of the dorsum of the penis. No inguinal or other glands were detectable, The mucous membrane of the mouth and anal region appeared to be normal and healthy. The mucoid urethral discharge (Gram stained) revealed scattered Gram positive cocci, numerous pus cells, a few epithelial cells and debris. Dark Ground examination showed common spirillae (of the coarse fusiform type), mixed with a few Treponema Pallida. The next day, after normal saline dressings, the Dark ground was repeated and showed many Treponema Pallida. Primary Syphilis was diagnosed, and procaine penicillin 1 mega daily

was given for 10 days. During this treatment the balanitis and lymphangitis of the penis settled down very well; the urethritis persisted for a while, showing only scanty milky discharge with a clear urine. On the eighth day urethral washing with 1/8000 oxycyanate of mercury was prescribed for one week. The urethritis rapidly disappeared. Blood taken frequently for W.R. amd Kahn reactions remained negative. The patient was discharged three weeks later. As I had never seen such a case before I diagnosed the patient as suffering from seronegative primary syphilis. I learned later, however, that the correct diagnosis should have been "syphilitic balanitis".(1)

According to Follmann (1943,) syphilitic balanitis is a primary manifestation of syphilis, and Gougerot thinks it is a precancerous lesion.

Treatment of the other 12 cases consisted of: dressings, and washing with: (1) methylated spirit, (2) normal saline, (3) 1/8 -10,000 oxycyanate of mercury, (4) sulphonamide powder. Simultaneously urethral irrigations with 1/8000 oxycyanate of mercury was recomended . Only 2 cases did not respond to this treatment and had some remaining urethritis. These two cases were infected with Gram positive cocci, sensitive to sulphonamides. A course of sulphatriad 4 gm. daily for 6 days cleared the urethritis completely.

In 6 cases in addition to normal involvement, (the glans penis and prepuce) the whole area of the external genitalia and scrotum with oedema and vesiculation of the skin occurred. This was caused by the use of condoms and pessaries by the consorts, and was in my opinion a contact dermatitis.

Three of these 6 cases were associated with acute urethritis. The incubation period of the contact dermatitis and urethritis lasted about 24 hours.

The urethritis in these three cases remained for some time, after the contact dermatitis had settled down well with calamine dressings. The discharge microscopically was typical for urethritis desquamativa. It was milky in colour, and smears (Gram stained) revealed large numbers of epithelial cells with myriads of organisms lying both free and intracellular. Leucocytes were rarely seen. In two cases there was pain on micturition, but the urine in all three cases was clear with only a few threads in the first glass. Investigation for Trichomonas was negative. There was no history of self medication, no previous attacks of any kind of discharge. Irrigations with normal saline cleared the urethritis in all three cases completely, though in one case the discharge persisted for seven weeks. No abnormalities were found on urethroscopic examination, which was carried out as part of the test of cure.

It would appear that all cases of balanitis complicated by urethritis should remain under observation for some time following clinical cure, and that tests of cure should be obligatory.

Another 8 cases of uncomplicated "urethritis desquamativa" with typical clinical and microscopical changes have been investigated. The majority of these cases did not require treatment as all symptoms settled rapidly and spontaneously. Only a few cases required irrigations with normal saline or weak solutions of oxycyanate of mercury to clear them. In 2 cases there was a recurrence of urethritis. In the first patient it was caused by masturbation, while in the second the condition appeared to be idiopathic.

In the preceeding paragraphs and Appendix, I have illustrated some of the diseases from the Balanitis and Miscellaneae Group, which were complicated directly or coincidentally by urethritis. Some of these diseases have been of venereal origin, while others have not. Several of them have been actual dermatoses.

As is made clear in Appendix, all cases of chronic urethritis, which do not respond in the normal way to treatment, should be fully investigated to exclude the presence of a stricture.

Conclusions.

This chapter emphasises one important point namely, that many cases of urethritis are secondary to a large group of diseases either of venereal or non-venereal origin. The diagnosis of N.S.U. of unknown origin would be made less frequently, if a full investigation was carried out to exclude those diseases, which often are the primary cause of the urethritis.

The presenting symptoms, which cause patients to seek advice are: urethritis and/or skin lesions.

When both of these symptoms are present, the patient becomes more apprehensive.

We approach now the question of who should treat these combined cases. Should it be the Dermatologist or the Venereologist ?. Frequently urethritis will not require any specific treatment e.g. in lichen planus, or psoriasis, because treating the skin disease will automatically clear the urethral discharge. In other cases (by a venereologist) treatment will play the principal role e.g. in balanitis. The simplest and most satisfactory solution of the problem, however, is close collaberation in these complicated diseases between the two groups of specialists.

IV. PART 2.

Gonorrhoea mixed with other organisms.(6,7,8,9,24).

Gonorrhoea is at present well controlled by penicillin, and there is no clinical evidence of the development of penicillin resistance by the gonococcus on any substantial scale. Many of the suspected resistant cases so far reported have proved on investigation to be due not to the gonococcus itself, but to a simultaneously acquired N.G.U. Those cases of gonorrhoea - uncomplicated with other bacteria, which do not respond satisfactorily to adequate doses of penicillin are due to two causes only: re-infection,and/or alcohol taken by the patient during treatment.

Complications in the form of posterior urethritis appear very rarely today. They are usually a consequence of: delayed report of patients to V.D. clinics, drinking habits (even beer), heavy work,and inadequate treatment often self-administered.

Epididymitis due to gonococci is in these days a rarity. In the last few years, I have seen only 4 cases of epididymitis in over 200 cases of gonorrhoea.

Description of these cases.

The first patient received the proper treatment for gonorrhoea,and next day he was imprisoned for some crime. In 3 weeks time while in prison,he developed bilateral epididymitis. Gonococci were in abundance in the urethral discharge, with both glasses of urine turbid. He denied drinking after receiving treatment.

The second case came from a prison in which he had spent one month. He denied sexual intercourse or drinking. Before he was sentenced he had received treatment for N.G.U.

namely sulphatriad tablets, which stopped his urethritis for a while.

On examination: there was a scanty purulent discharge, which revealed gonococci and he also had a right sided epididymitis. It is probable, that this patient had gonorrhoea from the beginning, but was misdiagnosed.

The third case: a labourer, aged 32, married, developed right sided epididymitis at the end of the third week after treatment for gonorrhoea. He has been attending the V.D. clinic regularly every week and denied intercourse or drinking; perhaps his heavy work produced the complication. Gonococci have been found in his scanty muco-purulent discharge and both galsses of urine were turbid.

The fourth case: a young boy, 18 years of age, on the fifth day after receiving penicillin injections for gonorrhoea, played football. During this game he received an injury to the left testicle, and did not finish the game because of pain. He was seen 2 days later in the V.D. clinic. He had an acute left sided epididymitis, and gonoccoci were found in the urethral smear together with Gram positive cocci and diphtheroids. The urine in both glasses was turbid.

All these 4 cases were treated with penicillin - 1 mega daily for 5 days. This dose of penicillin is usually very effective. In 10 - 14 days the epididymitis settled down completely, leaving only for a long time some hardness of previously infected lobes. This happened in 3 cases but the fourth case, in which the urethral discharge revealed mixed gonococcal infection took a much longer time to settle down. Diminution of inflammation was not so rapid, and the symptoms persisted. On several occasions a mild milky urethral discharge revealed Gram

positive cocci and bacilli -(post gonococcal urethritis.)). A course of sulphatriad tablets healed his urethritis in 1 week.

In the first 2 cases because of the conduct of the patients, there was some doubt about the truthfulness of their statements,denying fresh sexual intercourse or drinking. The latter case was probably misdiagnosed as N.G.U. on the first occasion,and the treatment by sulphonamide tablets was insufficient to clear the gonococcal infection, which must have been present from the start. But cases 3 and 4 are interesting. Their statement and denial of having fresh sexual intercourse or drinking after the treatment has to be accepted as the truth. Perhaps the heavy work in one of these cases, and the game of football in the other are the explanation for developing epididymitis. Therefore, our precautions and explanations to each patient receiving treatment for gonorrhoea should be repeated individually on each occasion. In a mixed urethral discharge (gonococci plus other organisms) complicated by epididymitis the administration of penicillin simultaneously with sulphonamide tablets seems to be the proper treatment. Another method is to give penicillin injections alone for 5 days,followed by streptomycin 1 gm. daily for 3 to 4 days. Such combined treatment in these cases does not produce post-gonococcal urethritis,and eliminates the epididymitis and urethritis in a much shorter time.

Urethroscopic examination as a part of the test of cure performed in several hundreds of cases of gonorrhoea revealed only a few abnormalities. Only 2 patients have been found to have real strictures, while another 3 cases have had "urethroscopic strictures". Many venereologists have abandoned urethroscopic investigations as a part of the

test of cure and use curved bougies. This is done only in those cases who have contracted gonorrhoea more than once.

Prostatic gland examination on the contrary to urethroscopic findings gives a different picture. In my 102 cases of pure gonococcal urethritis, prostatitis was found in 6 patients (5.9%) Group 1. In 37 cases of gonococcal urethritis mixed with other organisms prostatitis was found in 7 patients (18.9%) Group 2.

Similar findings have been observed by different authors (Waldermar E. Couts, Edna Silva - Insuna Santiago de Chile,[30] F.C. Bourgault Du Coudray and others)[10], since the introduction of sulphonamide and penicillin treatment for gonorrhoea.

The persistence of pus cells in the prostatic fluid indicates the existence of an infection. It is also characteristic of some of these cases, that the prostatic gland appears completely normal with no enlargement nor tenderness, but prostatic specimen showed pus cells, scattered or in clumps. In some cases there is a very mild tenderness or enlargement of the gland, which can be detected by rectal examination. In all these cases prostatic specimen was obtained following micturition and urethral lavage, and I was unable to find gonococci from the prostatic secretion microscopically or on culture.

In 2 of the 6 cases spirilla were found morphologically similar to Sp. dentium and in one case Trichomonas Vaginalis. In 3 cases from the series of 7 (Group 2) multiple Gram positive bacilli together with many pus cells were found. The remainder of the cases of both series revealed only multiple pus cells lying separately or in clumps.

The 2 patients with spirilla in the prostatic secretion were treated with arsenical therapy and responded satisfactorily. The one patient with Trichomonas did not return (defaulter). The 3 remaining cases from the Group 1 and 4 cases from Group 2 in which only pus cells in the prostatic secretion were found were treated with aureomycin capsules. This therapy was based on the opinion that the former micro-organisms could disappear by breaking up into coccoid or granular forms. The treatment consisted of aureomycin capsules 250mgm each four daily for 5 days. This treatment healed the prostatitis in 5 of the 7 cases. In all these 5 cases the prostatic gland was investigated 2 weeks after completion of the treatment, without endeavouring to obtain secretion. The glands were normal with no enlargement or tenderness, and no urethral discharge, both urines were clear. Two cases still showed some mild urethritis, which appeared at the end of the second week. In the smears (Gram stained) scattered pus cells and few saprophytes were found. Without touching the prostatic gland a second similar course of aureomycin capsules was administered (both cases admitted drinking heavily). Giemsa stained slides for inclusion bodies were negative. Four weeks later in both cases the prostatic glands were still tender. The secretions showed scattered pus cells. Mist. pot. cit. was administered in both cases and instructions about diet given. After 4 weeks the prostatic gland in one of these cases was tender and a few pus cells were still found in the secretion. Contact with the second case was lost.

The 3 cases from Group 2 in which Gram positive cocci and bacilli were present together with pus cells in the prostatic secretion, were treated with terramycin tablets

(250 mgm each 4 times daily for 5 days). Two cases responded well, and 3 weeks later their prostatic glands were normal. In the specimen of one of these cases there was a normal picture (2-3 pus cells in every few fields), while in the second case a specimen was not obtainable. The third case still revealed a tender prostatic gland, and clumps of pus cells were found in the smear. A second identical course of terramycin tablets was administered. Three weeks later the prostatic gland and smear were normal.

Of the 13 patients in Groups 1 and 2 with changes in the prostatic gland one patient became a defaulter at the start and a second one disappeared later. In 11 patients tests of cure were performed after 3 - 4 months and were completely satisfactory. All of these patients were instructed for their own sake to report to the clinic every 3 months. After a further 5 months only 3 of them had appeared. In 2 of them the prostatic gland and smears were absolutely normal, the third case (56 years of age) still had a tender prostatic gland and in the secretion 5 - 8 pus cells in each high power field were found. Prostatic massage once weekly was ordered, but after the fourth massage the patient defaulted. It is my opinion, that all cases of prostatitis should be investigated at least twice per year to observe their progress. Those cases who default may not have been completely cured and in the long run may require prostatectomy. This is particularly true of patients over the age of 50.

Patients with gonorrhoea simple or complicated do not pay much attention to their disease. Syphilitic patients cured and discharged, if asked to come once a year for blood investigation will do so willingly in most cases. The reputation and seriousness of syphilis is still dominant. It seems to be very necessary to issue instructions from the

proper authorities to induce patients with prostatitis to report to V.D. clinics for their own benefit, and to continue treatment until discharged as cured. Persuasion does not work. The adequate treatment of prostatitis would reduce the numbers of prostatectomies.

The incubation period in gonorrhoea now seems to be a little prolonged. In 128 patients aged 17 - 59, the incubation period varied from 2 - 8 days in 88 patients (68.7%) and in remaining 40 patients, from 8 - 18 days (31.3%). This is of no fundamental importance. It may only mean that there has been an alteration in the resistance of the mucous membrane of the urethra. On the other hand, however, it may indicate some adaptation of the gonococci themselves. No difference in the incubation period has been noticed in those patient, who have contracted gonorrhoea for the first time ,and in those who have had previous attacks. The ratio of primary infections to multiple infections was 3 : 2. These figures are dependant on the truthfulness of the patients.

For some years it has been observed that gonorrhoea, in which gonococci are mixed with other organisms has become much more frequent than before the sulphonamide/ penicillin era. These drugs have done much to establish the existence of primary mixed infections of gonococcal and non-gonococcal urethritis,since they are very effective in the elimination of gonococci, but are usually powerless in N.G.U.

The fact that some residual inflammation remains in a proportion of cases of urethritis following the elimination of gonococci by adequate penicillin therapy, suggests that the original infection was due to gonococci and other organisms which were penicillin resistant.

This was first noticed by A. von Wahl.[11] Gonococci ocurring in symbiosis vary in several respects from the normal gonococci. They are sometimes smaller, resembling organisms of the size of micrococcus catarrhalis. Sometimes they are bigger than normal. They stain with Gram stained pale-bluish colour. Often they are few in numbers compared with the other organisms. These variations cause difficulties in establishing the correct diagnosis under the microscope. In the same patient serial slides may give different pictures, and so faults in the technique of making and staining slides has to be eliminated. In these cases only culture can establish a proper diagnosis. Clinically these cases do not differ from pure gonococcal urethritis. The urethral discharge as a rule is always purulent or muco-purulent, the first glass of urine always turbid, and the second glass according to the duration of the disease clear or hazy. In 139 patients there were 19 cases (13.7%) in whom cultures had had to be taken to establish a proper diagnosis. In 1954 there were 2 cases. In 1955, 13 cases and in 1956, 4 cases.

Culture Investigations.

Specimens were collected into Stuart transport media,[12] which is also suitable for Trichominas Vaginalis, and laboratory investigations were performed in Glasgow Corporation Public Health Laboratory by Dr. J.L. Young.[13] These mixed infections of gonococci and other organisms, which are now much more frequent in males show some resemblance to the mixed non-gonococcal infections, ocurring in females. Most observers will agree, that a smear from an average mixed infection in a female always shows the presence of organisms with some morphological resemblance to gonococci. Many of these are Gram negative coco-bacilli, which often have a distinct tendency to coccal morphology

in exudates. De Bord[14] described many of the organisms, which may be mistaken for gonococcal microscopically. Neisseria other than gonococcal are not uncommon, but in culture their identity is readily eatablished. With reference to urethritis in males the same phenomenon occurs. In mixed infections in which the presence of gonococci are only suspected a diagnosis of "gonorrhoea" can not be made without culture. Because these mixed cases are relatively uncommon, it is better not to administer any treatment before laboratory investigation, as this takes only a few days. Penicillin administered before the laboratory result will definitely eliminate gonococci. It will eliminate also other organisms sensitive to it, but in those cases of mixed infections with penicillin resistant organisms, a post-gonococcal urethritis will inevitably occur. Delay in treatment for a few days will not harm the patient. It is not possible that immediate treatment with penicillin in mixed infections is producing N.G.U. at some later date.? In cases where the diagnosis is in doubt in following serial slides, the specimen for the culture should be obtained the following morning, when a fresh specimen will be available.

The individual antiseptic used in cleansing the meatus is unimportant. A sterile area is not obtained with any of the antiseptics in common use. I have found this on many occasions by microscopically examining superficial scrapings from the "so called" sterile area. There was little difference in the number of organisms encountered before and after cleansing. I disinfect the external meatus with any kind of antiseptic, which is in common use. With two pieces of sterile gauze between the index finger and the thumb of the left hand, the lips of the external meatus are opened and the loop, kept in the right hand,

is directed inside the meatus without touching the patient's glans penis. This method has proved very satisfactory.

Treatment of mixed Gonorrhoea.

The treatment of venereal diseases is regulated by the local authorities in each district, so too in the Glasgow area. The regulations relate chiefly to gonorrhoea, syphilis primary sero-negative and sero-positive. In the other stages of syphilis, the treatment is at the discretion of the physician. For a long time after the introduction of penicillin in the treatment of gonorrhoea, this disease has been treated with penicillin together with sulphatriad tablets. This combined therapy was reached after many years of trial and error. Since 1954 300,00 i.u. of procaine penicillin alone without sulphonamides was introduced as the treatment of gonorrhoea. In gonococcal urethritis this dose of penicillin so far is sufficient to eliminate the gonococci. As this dose can mask a coexisting syphilis, however, 3 months observations of W.R. and Kahn reactions is demanded. In those cases of mixed infections (gonococci plus other organisms) the addition of sulphonamides to penicillin seems to have a reasonable basis.

No. of Cases	Gonor-rhoea	Diphth-roides	Staph-albus	Coli-form	Staph.	Non-haem. strept.	Staph. aureus	Haemo-litic strept
37	37	14	8	6	3	3	2	1

The above table shows the bacteria, which were associated with gonococci in 37 cases of mixed urethritis. Although, each culture contained numerous types of organisms, only the predominant growth apart from gonococci is shown

in the table e.g. in 14 cases diphtheroides were the most profuse on the culture plate.

This group of 37 patients has been divided by the type of treatment given into two-sub-groups of 21 and 16 cases.

In the first sub group of 21 cases aged 19-51, 11 were single, 8 married, 2 separated. Six had been treated previously with penicillin for gonorrhoea, 1 for syphilis, and 3 for some skin infection. A Gram stained urethral smear showed: multiple gonococci, intra and extra cellular, and other organisms, which were classified by the naked eye as Gram positive cocci, bacilli and diphtheroides. In all these cases cultures were taken, and treatment was started immediately without waiting for the bacteriological results.

Treatment consisted of 300,00 i.u. of procaine panicillin, and 10 tablets of sulphatriad in one dose. In 13 cases the urethral discharge disappeared within one week together with such symptoms as: pain and frequency in micturition. The urine in all these 13 cases also became clear in both glasses, although in a few cases there were still light threads in the first glass. These disappeared completely in about 10 - 12 days. Some of the patients stated, that for about 2 weeks they observed a slight urethral discharge in the morning. Scrapings revealed no discharge. All these patients have been under regular observation for 2 - 3 months with no symptoms whatsoever until the test of cure.

In the remaining 8 cases from the group: the urethral discharge ceased in 5 cases completely after 2 - 3 days,

but recurred later after 7 - 12 days. In 3 of these cases the urethral discharge was scanty, muco-purulent and in 2 cases abundant and purulent. Microscopically in these 3 cases there were Gram positive cocci, bacilli, pus cells and some epithelial cells, but no sign of gonococci. In the other 2 cases: there were multiple gonococci and only a few other organisms which looked rather like saprophytes. These 2 patients confessed: to drinking, and one of them also had sexual intercourse. In the last 3 cases from this group of 8 the urethral discharge diminished, but never ceased completely. Several microscopical examinations of their urethral discharge revealed only Gram positive organisms.

Second cultures from these 8 cases are shown in the table below:

No.of Cases	Staph. albus	Coli-form	Diphth-eroides	Gono-cocci	*
8	3	2	I	2	

* With admixture of scanty staphyl.aureus and diphtheroides.

In the 2 cases with gonococci present in the discharge, 600,000 procaine penicillin i.u. was administered, plus 5 gms. of sulphatriad. The double dose of procaine penicillin was customary among Glasgow venereologists. The added dose of sulphatriad (5 gm. in one dose) became my own custom for cases with a mixture of organisms. The urethral discharge ceased in both cases completely. One case, when seen later, was symptomless, but disappeared before the test of cure; in the second case the test of cure was negative and the patient was discharged.

In the remaining 6 cases,two tablets of sulphatriad was given 4 times daily for 6 days. In 3 cases the urethral discharge ceased completely at the end of the treatment,and the patients were symptomless up to the test of cure ten weeks after the last treatment. In the other 3 cases the urethral discharge diminished markedly in one patient, while in 2 cases it ceased completely during the treatment,but recurred a few days after the treatment was completed. Microscopically in these 3 cases - Gram positive cocci have been found. For 2 weeks urethral wash with 1/8000 oxycyanate of mercury was prescribed three times weekly with some improvement, but in all 3 cases some Gram positive cocci were still found microscopically, although discharges were very scanty. A second identical course of sulphatriad tablets was prescribed. One case responded very well and remained well until the test of cure; in 2 cases there was a scanty persistent urethral discharge. On several occasions microscopically organisms were found,although,the urine was clear in both glasses with some threads in the first glass. Cultures in these 2 cases revealed coliform bacilli. Four capsules of chloromycetin daily for 6 days cleared the urethral discharges,and patients became symptomless up to the test of cure. One of these cases returned 4/12 later with fresh gonorrhoea.

The second sub-group consisted of 16 patients age: 18 - 51 years, 9 single, 2 married, 5 separated and widowers, 15 white, 1 - Hindu. Two of them treated with penicillin for previous gonorrhoea, 1 for syphilis and 2 for some skin disease.

Microscopically in all these cases gonococci with other organisms were present. All of them received 300,000i.u. procaine penicillin without any additional sulphonamides.

In 4 of them the urethral discharge ceased completely after several days, and these patients remained symptomless until the test of cure, and were subsequently discharged.

The remaining 12 patients of this sub-group showed:

a) pain, burning sensation and frequency on micturition; these symptoms diminished rapidly but persisted in a mild degree in almost all cases,

b) urethral discharge, (which diminished markedly in 8 cases and in 4 cases ceased completely for 2 - 8 days, but afterwards recurred again although not so profusely).

c) microscopically, in Gram stained slides in all these 12 patients there were Gram positive cocci, bacilli, diphtheroides, tetragenes, and in two cases intra and extra cellular gonococci.

Only one of these 2 with gonococci admitted to drinking. The second patient denied drinking or fresh sexual intercourse, but his reputation and frequent presence in V.D. clinic aroused some suspicion. Cultures from these 12 cases are shown in the table below:

No. of Cases	Staph. albus	Diphth-eroides	Coli-form	Staph.	Staph. aureus	Gono- cocci *
12	3	3	2	1	1	2

* With admixture of diphtheroides mostly.

The 2 cases of gonococcal urethritis again received 6000,000 i.u. of procaine penicillin plus 5 gms. of sulphatriad. In one of them urethral discharge ceased completely, he was

only 3 weeks under observation and then defaulted. In the second patient, the urethral discharge a week later still revealed some Gram positive cocci. Patient received a course of 4 gms. sulphatriad daily for 6 days. His urethral discharge settled down well, but 3 weeks later appeared again. In an abundant purulent discharge gonococci were found. The patient admitted that he had had fresh sexual intercourse, and had been re-infected. He received another 600,000 i.u. of procaine penicillin plus 5 gms. of sulphatriad tablets, and the urethral discharge ceased. The patient is still attending the V.D. clinic for treatment of a latent syphilis.

In the remaining 10 patients sulphatriad (4 gms. daily for 6 days) was prescribed. In 5 of these cases the urethral discharge settled down well, and the patients became symptomless up to the test of cure. In the remaining 5 cases the milky urethral discharge still showed Gram positive cocci, and lavage with 1/8000 oxycyanate of mercury in every second day for 2 weeks was prescribed. There was a temporary improvement in the urethral discharge. A second identical course of sulphatriad tablets was repeated. Only 1 patient responded well to this second course, and remained symptomless up to the test of cure. In the remaining 4 cases the urethral discharge reappeared again in 2 cases, and never ceased in the other 2. Culture from these 4 cases are in the table below:

No. of Cases	Negative	Coli-form	Staph. albus.
4	2	1	1

In the 2 negative cultures smears stained with Giemsa (prolonged stain) revealed only multiple pus cells and epithelial cells (a typical abacterial urethritis).

No inclusion bodies found, and cultures on special media for pleuropneumonia-like organisms were negative (sterile). These 2 cases were treated with 4 aureomycin capsules (250mgm each) daily for 6 days, together with 3 mgm one Vitamin 'B' tablet three times daily. Only one patient responded well to this treatment, and remained symptomless up to the test of cure. In the second case at the beginning of the third week after completeion of the treatment, the urethral discharge reappeared, and showed again abacterial urethritis. Investigations of his prostatic gland revealed, that the right lobe of the gland was tender and slightly enlarged, and in the prostatic smear multiple pus cells were found. This patient a few months later underwent a gastroenterostomy, and contact withhim was lost. In the remaining 2 cases 250 mgm chloromycetin 4 times daily was prescribed for the patient with coliform organisms, and terramycin 250 mgm 4 times daily for 3 days for the patient with staphylococcus albus. Both responded well and there was no recurrences in the 6 month period after the test of cure.

Urethroscopic examination done as a part of the test of cure in 35 patients revealed no abnormalities. In the 26 available prostatic secretions, the slides revealed normal pictures. In the rest of the cases the prostatic glands were normal (except for one described previously). The collection of specimens from the urethra was always taken with great care to avoid saprophitic contaminants. In each case, if necessary, several slides were taken to establish the identity of the mixed infection.

There was no selection of patient in both sub-groups (21,16 patients). They were simply treated as they come to the clinic.

Combined chemotherapy in bacterial infections.

The practice of combining two or even more antibiotic drugs in the treatment of patients is growing commoner. For various reasons these combinations often may be useful, but sometimes may be no better than one of the pair used alone. Occasionally the combination may be contra-indicated, because a diminished instead of an enhanced effect results.

Indications for combined therapy.

1) The urgent undiagnosed case - such cases really do not happen, or happen extremely rarely in venereal diseases.

2) Mixed and double infections:- a patient may have two separate conditions due to entirely different bacteria - e.g. urinary tract infection and lung infection. If it should be thought necessary to treat both together, no single drug may serve for both infections, and so two antibiotics may, therefore be needed.

3) Prevention of toxic effects: another possible indication for using two drugs is the danger of toxic effects from only one. In this category comes the use of sulphonamide combinations e.g. "sulphatriad". The advantage of this compound is, that each component retains its individual solubility in the urine, with the result that the risk of heavy crystalline deposition and consequent tubular or ureteric blockage is minimised.

These three indications are of much less

significance than the prevention of acquired resistance and the achievement of synergism.

Prevention of acquired resistance.

Acquired bacterial resistance is a change, which ultimately threatens to extinguish the usefulness of all the present antibiotics, especially penicillin. Its gradual development in communities, where these drugs are freely available, can be delayed in only 2 ways. The first of these is more discrimination, and restricted use of the drug, and to judge from experience hitherto, much cannot be hoped in this direction; the second is to combine the main drug with another having an adjuvant effect. The other may not only exert its own independent effect but prevent acquisition of resistance to the first. Sulphonamides act by blocking a stage in an essential synthesis of the development of the organisms, and other antibiotics probably act in a similar manner. The acquisition of resistance results from a circumvention of this technical process. If the second drug used blocks this circumvention, the alternative metabolic route cannot be established, and the organism, therefore, remains sensitive. If this explanation is true, it is remarkable, that so many combinations do act in this way, and it encourages the belief, that by this means itself more may be discovered about the points of attack of individual drugs.

Another advantage of combined therapy can be the achievement of an synergic effect. The definition of synergism proposed in 1952 by Jawetz and Gunnison, whose studies of combined drug effects have contributed so largely to our present knowledge, is: "a large increase in the rate

of early bactericidal action and the rate of cure of infections beyond that obtainable by simple additive effects of the agents".

Sulphonamide - Antibiotic Combinations.

Garrod in 1953[16] found, that sulphathiazole reduced the rate at which penicillin kills staphylococci. Penicillin is active only against multiplying bacteria, and another drug which prevents multiplication, therefore, removes a condition necessary for its full effect. The defect of this experiment, was that it was observed by viable counts over an eight hour period and so terminated too early. Others who have prolonged such experiments have shown,that the initial rapid decline produced by penicillin alone,may be succeeded by bacterial recovery, and actual growth, whereas the slower decline caused by penicillin and a sulphonamide continues and proceeds to ultimate extinction. Hobby and Dawson (1946) suggested, that this was due to the penicillin reducing the number of living bacteria to a level at which a sulphonamide could exert its full effect: the dependence of sulphonamide activity on bacterial numbers is well known. This is, therefore, not so much synergy in the ordinary sense,as two successive and complementary effects.

Jawetz and Gunnison 1952a[15] found,that antibiotics are divisible into two classes, group 1. (bactericidal): penicillin, streptomycin, bacitracin, neomycin; 2.(bacteriostatic):aureomycin, chloramphenicol, terramycin. Combinations within group 1 are often synergic,while within group 2, they are no more than additive. Combinations of the two groups are apt to be antagonistic, the group 2 drug interfering with the bactericidal action

of the other. Such antagonism is observed only, when the organism is fully sensitive to the bactericidal component; if it is somewhat resistant, the combination may actually be synergic.

It is strongly emphasised by Jawetz and Gunnison 1952b,[18] that no general rules about synergism and antagonism can be laid down. The same pair of antibiotics may exhibit either effect against different organisms, according to their numbers and sensitivity. Other authors have found, that the same pair may be either synergic or antagonistic against the same organism, according to the concentrations of the drugs used.[25]

The most frequent combinations of mixed infection in urethritis was that of gonococci with 1) diphtheroides, 2) staphylococci, and 3) coliform bacteria. In the combined treatment of penicillin and sulphatriad, the following results are obtained:

First group of 21 patients - 13 cases (61.9%) responded well. Second group of 16 patients - 4 cases (25%) responded well.

Conclusions.

From a comparison of the results of the treatment in these two groups the following conclusions can be drawn:

a) It is well known, that penicillin is an extremely efficient drug against: gonococcus, streptococcus haemoliticus, and non-haemoliticus, streptococcus viridans, but not against staphylococcus aureus, which quickly develops penicillin resistance.

b) In certain cases of mixed infection, the synergistic action of penicillin and sulphonamides, the latter even in small doses, gives good therapeutic results. This is especially so in the cases of gonococci mixed with diphtheroides, and to a certain extent in infections with gonococci and pigmented staphylococci. It seems to be reasonable, therefore, to use in mixed gonorrhoea a combined treatment of penicillin together with sulphonamides or other anti-biotics, to which the additional organisms are sensitive.

c) In all cases of mixed gonorrhoea culture and sensitivity test are obligatory, as microscopical examination is insufficient.

d) The selection and administfation of therapeutic agents should not be decided on microscopic examination of smears, but only used after culture and sensitivity testing of the bacteria. The only exception to this rule should be: sailors, who have to return to duty immediately, or those, who will certainly default if treatment is delayed, while waiting for the results of the laboratory tests.

In a mixed urethral infection attention should be paid equally to the other organisms, as well as the gonococci. Treatment should consist of penicillin and the other appropriate antibiotics. These patients should be under longer observation, and after satisfactory tests of cure should be told to report occasionally for periodic examination.

If the disease is explained to the patients, many of them will return, if any recurrences ensue. Otherwise complications may cause them to be investigated as fresh cases at other clinics.

From experience gained in the treatment of these 37 cases of mixed urethral infections, I have found, that it is now possible to treat and completely cure patients with identical mixed gonococcal and other bacterial infections of the urethra in a limited period of three months.

V. PART 3.

Bacterial Non-Gonococcal Urethritis (N.G.U.)[22,26,27,28].

Definition.

The criteria for the accurate diagnosis of "classical" Bacterial N.G.U. are the microscopical demonstration of at least two different species of non-gonococcal bacterium in a direct smear, and the cultural identification of these organisms.

Etiology.

Factors in Bacterial N.G.U. of aetiological significance are:-

a) Unsettled sexual life (batchelors, widowers, and separated.)

b) Poor hygiene.

c) Alcoholic excess.

d) Other infective diseases (either bacterial or viral), which lower the general resistance.

e) Congenital deformities e.g. hypospadias.

f) Prostatitis - proven, and also the so-called "asymptomatic" variety.

g) Strictures.

Investigations.

In every case the following investigations were carried out.

1) Urethral discharge examined for organisms (Gram stain).

2) Dark Ground - for Trichomonas and Leptospirilla.
3) Culture for organisms including Trichomonas.
4) Testing organisms for antibiotic and chemotherapeutic sensitivity.
5) Urinary reaction test.
6) Prostatic smear for prostate and/or duct infection (P/S).
7) Urethroscopy - except in very acute type (U/scope).

After these investigations were completed - treatment was begun.

One hundred and seven cases of apparent Bacterial N.G.U. and 43 controls were investigated. The latter group was composed of patients reporting to V.D. clinic with conditions such as: pityriasis rosea, psoriasis, condylomata accuminata etc., and also patients reporting to the Skin Out-patient Department. In none of the control group was recent sexual intercourse admitted, and there were no complaints or evidence of any urethral discharge. General details of these two groups are analysed in the below table.

Details	Bacterial N.G.U.	Controls.
Age Limits	18-57 (59 between ages 35-42).	16-53
Marital State:		
Married	20	9
Single	61	26
Widower or separated	26	8
No history of previous V.D.	76(71%)	38(79.1%)
Previous history of Gonorrhoea	31(28.9%)	4(9.3%)
Total		
Once	19(17.7%)	
Twice	8(7.4%)	
More than twice	4(3.7%)	
Previous history of Syphilis	5 (2 unsuspected)	1

The findings of cultures of urethral discharges in the 107 cases of Bacterial N.G.U. are given in the next table.

No. of Cases	Diphtheroides.	Staph. Alb.	Staph. aur.	Pigment staph.	Staph.	Coliform	Non-haem. Strept.	Haem. Strept.	Gonococci*	Strept. virid.	Trichomonas
107	36	27	5	10	9	6	6	1	5	2	0

* These five cases of gonorrhoea have been eliminated from the group, and reduced the number in the group to 102 cases. So all percentage are calculated on 102 cases.

In the above table only the predominant organism is given in each culture. Many of the cultures were mixed, the most common combinations were: staphylococcus and diphtheroides - 27 cases (26.4%), (staphylococcus albus was the most frequently ocurring organism followed by pigmented staphylococcus; staphylococcus aureus only in two cases (1.97%); staphylococcus aureus alone three times (2.9%); coliform bacilli plus staphylococcus albus four times (3.9%); coliform alone twice (1.97%); non-haemolytic streptococcus five times together with diphtheroides (4.9%) and once with staphylococcus (0.98%); streptococcus viridans twice only alone, and almost in pure culture (1.97%).

In five cases the presence of gonococci which was difficult to identify on direct microscopic examination was confirmed by culture. In 4 cases the gonococci was intermingled with numerous pigmented staphylococci and diphtheroides, and in one with staphylococcus albus. The provisional microscopical diagnosis in 3 of these cases was: diplococcus of Rosenthal (the pseudo-gonococcus) and in the other 2 cases; micrococcus catarrhalis.

The 31 patients (30.4%) who had previously had gonorrhoea, had been treated with penicillin and the majority had sulphonamides as well. Only 15 patients denied having had sexual intercourse during the preceding 3 - 5 months. The majority had had intercourse during the previous few days-to one month. In 8 patients (7.8%), who completed this treatment for gonorrhoea 3 -8 weeks previously, and who denied subsequent intercourse, the urethritis must be accepted as: post-gonococcal urethritis.

Primary bacterial urethritis of venereal origin is usually contracted from women suffering from leucorrhoea, by sodomy, and occasionally by oral coitus. In my series it was not possible to assert that sodomy or oral coitus were causes. In six cases in which coliform organisms were found (4 cases - coliform plus staphylococcus albus, and 2 cases coliform alone) cultures from the anal canal were also taken with negative results.

The French school claim that Aubert in 1884 (Harkness 1950)[2] was the first to demonstrate, that there occurred urethral discharges due to bacteria other than gonococci. This author described 3 cases of non-gonococcal urethritis. His observations led him to believe, that a special type of urethritis characterised by the presence of organisms other than the gonococcus did exist, and that the discharge could be so slight as to be easily overlooked, but the infection nevertheless could cause complications such as cystitis and epididymitis.

Many workers following Aubert reported further cases due to organisms other than gonococci: Bockhart 1886,

Rauzier, Legrain, Hogge, Guiard, Janet and Barlow. It was Barlow's contention that, "where there was a previous history of gonorrhoea, or where such complications as strictures were present, every urethritis should be regarded as gonococcal; and that before a diagnosis of N.G.U. was made, any organisms cultivated should have been examined for pathogenicity in the male urethra". Present day opinion about this matter is distinctly different especially regarding the first part of Barlow's assertion (strictures). There are many venereologists, who still maintain, that there is no such disease as N.G.U., and that the gonococcus is always lurking in the background. The advent of sulphonamides and penicillin during the past 15 years, has lessened that opinion on the one hand, but on the other hand it has been suggested (by some workers), that penicillin itself is responsible for the increase in the incidence of N.G.U. There are many difficulties in determining the pathological significance of organisms seen in smears or grown in cultures from the urethral discharge in N.G.U. These organisms may be either saprophytes with no pathological implications, or they may be directly responsible for the infections.

The urethra proximal to the fossa navicularis is sterile in healthy persons. The mucous membrane of the prepuce, glans penis, the external urinary meatus, and fossa navicularis normally harbour many varieties of organisms: staphylococci, micrococci, diphtheroid bacilli, streptococci - haemolytic and faecalis, Rosenthal's large diplococci, smegma bacilli and various types of spirochaetes. Their number depends partly on the cleanliness of the individual. All these organisms are easily found in the urethra of male patients, who do not complain of any urethral discharge. They may come to V.D. clinics with

various skin diseases (pityriasis rosea, psoriasis, dermatitis, condylomata accuminata and others). Very often their last sexual intercourse was a long time ago. From this group some of the control patients were chosen, and some also from patients in Skin Out-patient department.

The control group consisted of 43 patients. In all of them urethral swabs were taken, in some of them swabs from the preputial sac with only the mildest balanatis. The bacteriological results of this group are in the table below.

No. of Cases 43	Staph.	Diphtheroides	Strept haem-olytic	Micro cocci	Rosenthal's	Smegma bacil.	Spirochaet	Sterile	%
Urethral Swabs 34	10	9	2	3	2	-	-	8	76.5 bact. 23.5sterile
Swabs & scraping from prep-utial sac 9	-	-	-	-	-	6	3	-	

Examination of urine - was limited in each case to testing with litmus paper. (Both groups together - 145 patients). In 129 cases the urine was acid - in 16 cases alkaline. In these 16 cases the urine was investigated on the next visit and showed an acid reaction in 14 cases (previously alkaline reaction was due probably to the food). The urine in the other 2 cases remained alkaline on several occasions (both cases from the group of 102). One gm. Ammonium Chloride daily for one week, converted the urine to the normal acid reaction. One of these cases with alkaline urine had had a chronic, milky, urethral discharge - microscopically showing quite a number of Gram positive cocci, pus cells and spithelial cells. The urethral discharge disappeared completely when his urine became acid.

Prostatic gland investigations: as a rule the prostatic gland in these patients (group 102) was not investigated during treatment. The finding of organisms in the urethral discharge was, for me, sufficient to establish the diagnosis of "Bacterial Urethritis", although, in rare cases turbid urine in the second glass indicated, that the prostatic gland might be the source of infection. Unnecessary interference such as: investigation of the prostatic gland or urethroscopy (except a few cases for "experimenti causa") - was avoided, until proper treatment had caused the acute or sub-acute phase to subside.

In only 7 cases, in which urethral discharge persisted in spite of the treatment were prostatic gland investigations carried out. Examinations were made approximately 3 - 4 weeks after the institution of treatment, and about 5 - 6 weeks after the first symptoms of the urethral discharge appeared.

In 6 cases the prostatic glands were slightly enlarged and tender, and numerous pus cells were found microscopically; on culture 5 were sterile, and one showed pigmented staphylococci. The latter case showed normal gland and microscopically normal prostato-vesicular fluid. As a rule and as part of a test of cure prostatic gland investigations were done in all cases (from the group of 102 - in 51 cases plus 7 described before = 58 cases 56.8%,) the other patients ceased attendance during treatment, and did not return to the clinic. In another 5 cases (from the 51) the prostatic gland examination revealed some enlargement and tenderness, and prostato-vesicular fluids showed only abnormal numbers of pus cells lying separately and in clumps without accompanying organisms. Cultures became negative (these 5 cases had been suffering from "asymptomatic prostatitis".).

From the control group of 43 patients (only 23 were fully investigated - the rest defaulted) in only 2 cases were changes found in the prostato-vesicular fluids - namely numerous pus cells. They had also been labelled "asymptomatic prostatitis".

Thus from the first group of 102 cases - 11 cases (10.8%), and from the control group of 43 cases - 2 cases (4.6%) revealed changes in their prostatic glands and prostato-vesicular fluids.

Strictly speaking from the 102 only 58, and from 43 (controls) only 23 have been investigated. Altogether 81 cases were investigated, and changes were found in the prostatic glands in 13 cases (16%) - (7 - "asymptomatic").

In the chart below are the findings in the prostatic glands in all the groups of patients seen by me in this research.

Prostatic gland investigations and findings.

NO.of Cases	Disease	Prostatitis	%
102	Gonorrhoea	6	5.9% 6 in 102=5.9%
37	Gonorrhoea mixed with other organisms	7	18.9% 7 in 37=18.9%
102(58 1)	Bacterial Non-Gonococcal Urethritis(B.N.G.U)	11	18.9* 11 in 102=10.8% 11 in 58=18.9%
43(23) 2)	Controls	2	8.7%* 2 in 43= 4.6% 2 in 23= 8.7%
58(23) 3)	Bacterial Non-Gonococcal Urethritis and controls	13	16%* 13 in 81= 16%
103(82) 4)	Abacterial Urethritis (A.U.)	27	26.2%* 27 in 103=26.2% 27 in 82 32.9%

* These percentages represent the percentage of cases of prostatitis out of the total number of cases in each group, who completed their investigations and treatment (the figures in brackets).

From 27 cases (9 cases from the Hecht sub-group and 18 cases from the Waelsh sub-group of urethritis) 13 of them have been "asymptomatic" (4 in Hecht sub-group and 9 in Waelsh sub-group).

Urethroscopy was performed in 5 cases (of 102) and in 2 cases (of the 43 controls) in which in spite of lack of urethral discharge multiple gram positive cocci were found on cultures from scrapings "experimenti causa"; the urethroscopic picture in all the 7 cases was very similar to that seen in gonococcal urethritis viz. some redness and inflammation and quite often soft sub-mucous infiltrations. These soft infiltrations were seen chiefly on the lateral walls and on the roof of the urethra. They presented as pale, pearly-grey, gelatinous tumours of varied size, sometimes confluent projecting into the urethral tunnel, and appearing to rise from the sub-epithelial connective tissue. They were indistinguishable from those seen on gonorrhoea, but they were fewer in number, which fact perhaps explains the rarity of the subsequent development of hard infiltrations and strictures. Urethroscopy performed as a part of test of cure in another 47 cases (from both groups), revealed normal picture in all cases, except some mild redness in few of them; no strictures were found.

There have been no such complications as epididymitis during the investigation in either group. In the first group (102 patients) hernia-inguinalis was found in 2 cases and hydrocele in one case. In the control group (43 patients) one varicocele and one hernia-inguinalis was found. Two patients from the first group and one case from the control group confessed, that many years ago they had had epididymitis following gonorrhoea

(in one case of each group) the third case from the control group denied gonococcal infection, he had had some bicycle accident and as a consequence of that developed right epididymitis.

The incidence of bacterial urethritis of venereal origin is in my experience much higher than that in which no organisms are found. The following tables show this for each clinic and year from 1950 - 56.

Broomielaw Clinic.

Year	Bacterial Non-Gono-coccal Urethritis.(BNGU)	Abacterial Urethritis(A.U.)	%*
1950	183	39	21.3
1951	156	41	26.2
1952	169	74	43.8
1953	198	48	24.2
1954	207	72	34.8
1955	150	48	32
1956	229	160	69.8
Total	1265	482	37.3

* abacterial compared with bacterial.

Black Street Clinic.

Year	Bacterial Non-Gono-coccal Urethritis(BNGU)	Abacterial Urethritis(A.U.)	%*
1950	155	108	69.7
1951	106	98	52.7
1952	160	108	67.6
1953	158	95	60.1
1954	121	95	78.4
1955	99	78	78.8
1956	273	138	50.5
Total	1152	740	64.2

Paisley Clinic.

Year	Bacterial Non-Gonococcal Urethritis (B.N.G.U.)	Abacterial Urethritis (A.U.)	%*
1950	66	40	60.6
1951	34	19	55.9
1952	47	29	61.7
1953	49	25	51.0
Total	196	117	59.6

The total number of cases seen at the three clinics during the period was:-

Bacterial Non-Gonocaccal Urethritis (B.N.G.U.) - 2613
Abacterial Urethritis (A.U.) - 1339

= 50.7%

The proportion in separate clinics and years increases from 21.3% upto 78.8% but averages 50.7%

The incubation period of bacterial urethritis is usually longer than in simple gonorrhoea, but is the same as that in gonorrhoea complicated by other bacterial infection. It is approximately from 4 - 8 days; only a few cases were seen, which developed a discharge 2 - 3 days after exposure to infection. The incubation period is certainly much shorter, than in Waelsh urethritis. In a few cases of hypospadias the incubation period was very short. When the non-specific immunological barrier of the fossa navicularis is lacking, as it is in all cases of hypospadias, (the distal end of the urethra then being lined with stratified columnar or pseudo-stratified columnar epithelium), infection is more likely

to occur. The signs and symptoms are then more rapid in their development.

The clinical features of Bacterial Urethritis are characterised by muco-purulent or purulent discharge which is not so profuse as in gonorrhoea. It is clinically indistinguishable from gonorrhoea. Itching and burning sensations at the distal end of the urethra are more marked during micturition. Sometimes there is some swelling of the lips of the external urinary meatus due to prolapse of inflamed mucous membrane. In neglected cases and very occasionally in acute cases, local symptoms are more severe, especially, when the posterior urethra is involved. There may be frequency of micturition, pain, during or at the end of micturition, and sometimes haematuria at the end of micturition.

The urine in the "two glass" test is turbid or clear with threads in the first glass, and clear without threads in the second glass; in neglected cases the urine is turbid in both glasses.

Methods of Examination.

When making the diagnosis the results of examination of smears and of cultures of the urethral discharge should always be included. The venereologist finds that in acute gonorrhoea cultures are rarely necessary, unless there is mixed gonorrhoea. In primary urethritis due to non-specific organisms, however, they are very essential not only in the diagnosis, but especially in controlling treatment. Together with cultures, antibiotic sensitivity tests should be performed. It is also very important

to establish the time, when the patient last passed his urine. Only a few experienced patients are aware, that they should not pass urine for at least a few hours before the consultation. If this precaution is not observed, it is better to postpone the examination of smears, and the taking of material for cultures until the next day. It will not harm the patient and by this procedure an eventual primary gonococcal urethritis will not be overlooked, and a correct diagnosis of N.G.U. (bacterial or abacterial) rightly established.
The importance of thorough cleansing of the glans penis and fossa navicularis with spirit before taking specimens for both smear and culture examinations must again be emphasised. It has already been mentioned that sterile gauze should be used after cleansing, to prevent even the cleansed skin of the glans penis and mucous membrane of the external meatus from contaminating urethral discharge. If this precaution is not observed it is possible for saprophytic organisms to contaminate an abacterial or bacterial urethral discharge. This will give rise to error, especially in the diagnosis of abacterial urethritis.

To establish an accurate diagnosis of bacterial urethritis, two or three smears if necessary must show large numbers of pus cells as well as organisms, which are both intracellular and extracellular in position, and the culture must yield a profuse growth of one or more organisms. A few scattered organisms in smears and scattered colonies in cultures are in all probability due to inadequate cleansing. Antibiotic sensitivity tests should be carried out in all cultures, and the coagulase test in cultures yielding staphylococci.
The effects of treatment with sulphonamides or antibiotics

will confirm the diagnosis of bacterial urethritis in cases in which organisms susceptible to these drugs are responsible for the infection.

In both groups, at the first visit blood was taken for Laughlan and Gonococcal Complement Fixation Test, the latter only in these cases, who had previously had gonorrhoea. In the last eight years G.C.F.T. has been found positive in one case only, in spite of blood being taken for this test from every suspicious case. He was a man 42 years of age, separated, had gonorrhoea nine years previously, without any signs or symptoms of any kind of venereal or non-venereal diseases on examination. Two years ago, he was treated in England for N.G.U. - blood taken at that time was positive for G.C.F.T. His urethritis was healed in a few weeks but the G.C.F.T. still remains positive. It seems that G.C.F.T. is now of less value and significance than previously. According to some venereologists this test has today almost lost its validity. All cases of true Bacterial Urethritis (N.G.U.) confirmed by smears and cultures require also the same general principles of treatment for gonorrhoea, namely:- rest, avoidance of trauma, no alcohol or sexual excitement, abstinence from cycling, horse-riding and athletics. Neglect of these principles not only delays cure, but may also cause complications - both local and blood-born. No complications have been observed in the series described above, not even in those cases in which some investigations were performed "experimenti causa". This may have been, because treatment in thses cases was instituted almost immediately after the investigations.

The prognosis of Bacterial Urethritis of venereal origin is good, especially when compared with that of

Abacterial Urethritis. Sometimes the cure is rapid occurring in 2 - 3 days, but it depends largely on the type of organism responsible, and on its susceptibility to treatment.

Treatment.

As a rule all cases of true Bacterial N.G.U. require treatment. In some cases with a short incubation period, a mild urethral discharge, in which smears contain scattered organisms and some pus cells, and the first urine glass with slight haziness or even clear with threads - urethro-vesical irrigations of 1:8000 oxycyanide of mercury is quite sufficient treatment. In some of these mild cases, with more than one species of organisms present, urethro-vesical irrigations together with a 4 to 7 days course of sulphonamides(providing the organisms are sensitive on laboratory investigations) is usually curative.

This treatment should be ordered immediately for all those patients who, like sailors for example are going away in a few days, or others, who live far away and cannot attend the V.D. clinics frequently and regularly, and cannot wait, even for a few days, for the bacteriological results.

In the groups of 102 cases - 49 cases (48%) have been divided into two sub-groups as regards treatment. The first sub-group of 21 cases were treated with sulphatriad tablets 1.0g. 4 times daily for 4 days, the second sub-group of 28 cases with the same dose for 7 days.

In seven cases (6.8%) course of sulphatriad was 1.0g. 3 times daily for 4 days together with urethro-vesical irrigations and in 9 cases (8.8%) urethro-vesical

irrigations were used alone.

These forms of treatment were arranged in the 65 cases (63.7%) without any segregation of patients, and before receiving the reults of the cultures and sensitivity tests.

In the other 37 patients (36.3%) from the group of 102 cases, treatment was withheld until the results of cultures and sensitivity tests were available.

The only sign, which permitted me to order the treatment in those 65 patients, was the microscopically proven absence in all smears (Gram stained) of several species of mixed organisms. The increase or reduction of doses of sulphatriad was dictated by the fact, that many patients complained of different side-effects with this drug - namely, headache, nausea, depression, occasionally sensitisation rashes.

The results of treatment are summarised in the accompanying table.

	No. of cases	Cured	Defaulters	Not Cured	% +ve	Treatment
1st sub-group.	21	14	5	2	66.6	Tabs. Sulphatriad 0.5gm. x 2 x 4 -four days.
2nd. sub-group.	28	20	7	1	71.4	Tabs. Sulpha-triad 0.5gm x 2 x 4 - seven days.
3rd. sub-group.	7	3	4	-	42.8	Tabs. sulph. 0.5 x 2 x 3 for four days + irrigations.
4th sub-group.	9	1	6	2	11.1	Irrigations alone.
Total	65	38	22	5	58.4	

In the first sub-group of 21 cases, 12 cases responded very well to treatment. In four cases a second course of sulphatriad was administered two weeks later. Two cases responded very well, and became symptomless, and remained so up to the test of cure. The other 2 cases had several recurrences and were treated with urethro-vesical irrigations and different antibiotics, but their moral conduct was not high, and they were drunkards. Urethroscopic and prostatic investigations in these 2 patients did not reveal any abnormalities. One of them is still attending the clinic suffering from latent lues. Only two cases complained of some nausea and mild depression, which ceased completely after the end of treatment.

In the second sub-group of 28 cases, 18 cases responded well to one course of sulphatriad (7days); two cases required a second course and the last case eventually responded to chloramphenicol. Three cases complained of headache during the first course, and one case complained of rather severe depression at the end of the second course, but in spite of that he completed treatment.

In the small group of 7 cases treated with sulphatriad tablets combined with urethro-vesical irrigations all 3 followed up cases remained symptom-free up to the test of cure.

In the group of 9 cases treated with urethro-vesical irrigations alone, the 3 cases followed up became symptomless after daily irrigations, and remained so for about 2 to 3 weeks. Recurrenee of urethral discharge occurred in all 3 cases. After further treatment with

sulphatriad for 7 days, one case responded. In the second case an urethral stricture was found. The third case with "asymptomatic prostatitis" responded very well to aureomycin.

In the other 37 cases (from 102) the delay in treatment did not exceed one week. The results are shown in the accompanying table.

Treatment of B.N.G.U. with Antibiotics and Sulphatriad Tablets.

	No.of Cases	Cured	Defaulters	Not Cured	%+ve	Treatment
1st.sub-group.	16	12	3	1	75.0	Aureomycin caps. 250mgm x 4 for 5 days.
2nd.sub-group.	6	4	2	-	66.6	Chloramphenicol caps.250mgm x4 for 6 days.
3rd. sub-group.	15	9	5	1	60.0	Sulph.Tabs. 0.5gm. x 2 x 4 for 6 days.
Total	37	25	10	2	67.5	

As a result of past experience treatment prescribed consisted of aureomycin, chloramphenicol or sulphatriad. Aureomycin 250 mgm 4 times daily for 5 days, together with Vitamin B, 3 mgm 3 times daily was prescribed in cases in which staphylococci: albus; pigmented, non-haemolytic and haemolytic were predominant in the culture, and were sensitive to that antibiotic.

Sixteen cases were so treated and 10 responded very well. In 6 cases recurrences occurred; in 2 cases

the discharge reappeared a few days after completion of the treatment, and in 4 cases 3 to 4 weeks later. In three of these 4 cases there was a suspicion of reinfection. Aureomycin was repeated, but only 2 cases responded well to this course, four relapsed, and were treated with urethral irrigations. Three of them became symptomless, but defaulted later on. The other case is still attending the clinic suffering from latent lues and occasional recurrences of urethritis.

Six cases with coliform bacilli were treated with chloramphenicol (250 mg 4 times daily for 6 days). Five of them responded very well to the first course. In one case recurrence appeared about two weks after the completion of treatment. This patient responded well to a second identical course, but this patient and another disappeared from the clinic before the test of cure, thus reducing the number to 4 cases only.

Fifteen cases, in which diphtheroid bacilli were predominant in cultures, received a course of sulphatriad tablets (1.0g 4 times daily for 6 days). Two of them did not appear after the completion of treatment, 8 responded well to the course. In five cases the course was repeated as soon as the urethral discharge reappeared in 6 - 14 days. One case responded well to the second course, and another 3 patients ceased to report so that there were 5 defaulters in this group. The last case relapsed about 10 days after completion of treatment. Aureomycin eventually cleared his urethral discharge and he remained symptom free to the test of cure.

If the second course of sulphatriad does not cure Bacterial N.G.U., this drug should be abandoned and urethro-

vesical irrigations administered for 2 to 3 weeks. Later on some other antibiotic should be prescribed if necessary. Cases have been observed in which sulphonamides prescribed to the patient after positive sensitivity test stopped the urethral discharge for a while only. If the second course of sulphonamides does not stop the urethral discharge the explanation is, that the bacteria have become resistant to the drug. I observed only 2 such cases in my work.

Of one hundred and two cases treated, only 63 cases (61.7%) continued to the test of cure, 39 cases (38.3%) defaulted. The high pereentage of defaulters has to be explained. In some of them the urethritis probably ran a mild course, and did not bother them much; in some others e.g. sailors, conditions of their work or remoteness from the clinic, prevented them from continuing treatment. Some of them, knowing that their disease was not of venereal origin, disregarded treatment. But the large percentage of those patients, who persisted with treatment, did so, because of the acuteness of the urethritis or because of recurrences. These patients endured the period of treatment and observation.

Discussion.

It appears from the above analysis, that sulphonamides play an important role in the treatment of true Bacterial N.G.U. In 47 cases out of 63 (74.6%) a satisfactory result was obtained. This percentage could be increased, if the treatment were temporarily withheld, until receipt of the results of culture and sensitivity tests. Success depends largely on the type of organisms responsible. Because of difficulties in the correct bacteriological diagnosis in direct smears seen under the microscope, cultures and sensitivity tests are very essential.

Infection due to diphtheroid bacilli, haemolytic streptococci and staphylococcus aureus, usually show rapid improvement and cure with sulphonamides. Aureomycin therapy has a beneficial effect in all staphylococcal infections, as does chloramphenicol in coliform bacilli infections. Penicillin was not administered in the present series of Bacterial N.G.U. even in positive sensitivity tests, because of past experience of unsatisfactory results. The same can be said about streptomycin, the beneficial effects of which are, however, much greater in Abacterial Urethritis.

From the control group, who were largely seen in the Out-patient Skin Department, 3 cases became patients in V.D. clinics, suffering from true Bacterial N.G.U. Two were married, 1 single, the latter pateint denied sexual intercourse for a long time. He had previously had gonorrhoea, as had one of the married patients. In two cases cultures showed multiple diphtheroid bacilli together with other organisms, in one case - streptococcus haemolyticus was predominant. All three cases responded well to sulphonamide therapy.

My personal opinion is, that those three patients who denied fresh intercourse are to be disbelieved because of their character. As is very well known and has been proved in the control group many "so called" healthy people, harbour different organisms inside and outside the genital organs. Only some of them suffer from urethritis, and they probably do so because of other general infections or virus diseases, general debility, undernourishment, alcoholism, poor hygiene and excess in sexual life.

All cases of true Bacterial Urethritis require treatment varying from urethro-vesical irrigations alone

to combined treatment with sulphonamides and antibiotics, including prostatic massage in some cases. On completion of the treatment, test for cure should be done routinely. Not every case requires a full test. In some cases the test must show, that the urethral discharge has disappeared completely, that the urine in both glasses is clear with no threads, that the curved sound passes the whole urethral canal, and that serological tests for syphilis before and after treatment are negative. If at the beginning and during treatment only the first glass of urine showed turbidity, then it is sufficient to examine gently the prostatic gland without expressing prostatic secretion. If both glasses of urine were turbid, urethroscopic and prostatic secretion investigations must be performed as a test for cure. Generally the prostatic gland was investigated during treatment in every case, who confessed to previous contraction of gonorrhoea or urethral discharge.

It is astonishing how often the prostatic gland is involved during Abacterial and Bacterial (N.G.U.) Urethritis, and how seldom it requires special treatment. Usually the treatment prescribed, i.e. sulphonamides or antibiotics, heals the inflammation of the prostatic gland rapidly. Diet and the general principles of treatment: non-indulgence in alcohol and sexual excitement, abstinence from cycling and horse-riding play a big role. In a few cases only sitz-bath or short wave diathermy helps considerably. Prostatic massage should be done only in resistant cases and they are very few. All those patients who have had any prostatic involvement even if, on the completion of the treatment, everything was found to be normal, should be advised to report at least twice per year for observation. This applies to

to patients of advanced age.

Conclusions.

Each case of Bacterial Urethritis (N.G.U.) has to be very carefully investigated to establish the correct diagnosis. In many instances this diagnosis is much more difficult than in gonnrrhoea. Examination of several smears (slides) in each case, culture, and sensitivity tests are all necessary. Cleansing of the external meatus is essential. Prostatic gland investigation is of great importance and value, especially in cases, with recurrence of the urethral discharge, and in cases who previously have had gonorrhoea.

In true Bacterial (N.G.U.) Urethritis, treatment is as a rule indicated. Some of these cases can be treated (mixed organisms) and have to be treated (sailors going soon abroad), before cultures are obtainable. In the remaining cases treatment should be recommended, when culture results and sensitivity tests are available. The general principles (as for gonorrhoea) must be observed. Treatment, observation and test of cure must be on the same level as in gonorrhoea. Patients must be warned about the consequences and complications, if they do not obey instructions. If possible their consorts should be investigated and treated simultaneously.

A correct diagnosis based on clinical observation, microscopical examination, culture and sensitivity test and correct treatment will cure the patient in a short time, and exempts him and the doctor from trouble from recurrences. By doing so urethritis of this group can be greatly reduced in frequency.

VI. PART 4.

Abacterial Urethritis (82-92)

It has been customary for some time to divide Non-Specific Urethritis into Bacterial and Abacterial Urethritis, depending on, whether or not bacteria are seen in the urethral smears. It is very well known, that mixed gonorrhoea (gonococci + other organisms), treated with some antibiotics, especially with penicillin, leaves a Bacterial (N.G.U.) Urethritis resistant to that antibiotic. It is also well known, that Bacterial (N.G.U.) Urethritis appears quite often as an original inflammation of the mucous membrane of the urethra, as a consequence of the sexual intercourse, including oral or anal coitus. And it is also known, that in a large percentage of "so called" normal people, we find one or several different bacteria in their urethral scrapings.

We see such people in the Skin or Venereal Diseases Clinics. The Skin Clinic patients never complain of any urethral discomfort, and are usually used for our "control" group. If hygiene is lower, the percentage of cases showing different kinds of bacteria in these "control" groups is higher. Therefore, it is considered that "Bacterial (N.G.U.) Urethritis" is not a common entity, and that the bacteria found are usually commensals.

Why do these organisms, which are in such a large percentage "comensals", produce in some instances urethral discharge? The answer is, that the overwhelming number of these individuals, are unmarried, and have little stability of their sexual life, as occurs with marital relationship, and their exposure or sexual activity is on a

"hit and run" basis. It is conceivable, that as a result of this irregular type of sexual activity, alterations such as change of pH., modified enzyme systems, poor drainage or lowered local tissue resistance may occur in the prostate (25 - 30% of these patients have silent "asymptomatic" chronic prostatic inflammation.). Inflammation of other urethral glands, which favours the progression of a previously quiescent inflammatory process, may take place. The excessive use of alcohol shortly before the appearance of discharge is such a frequent observation that it, too, cannot be disregarded as a predisposing factor. Alcohol could act in two known ways, possibly more. It could decrease local tissue resistance, or it could affect the secretory activity of the prostate gland, resulting in increased amounts of prostatic fluid, or congestion, depending on the potency of the prostatic tubules.

Excesses in cycling and horse-riding, or acute infection elsewhere in the body, are often precursors of urethritis. This suggests that, on occasion, virulent organisms reach the accessory urethral glands through the urine or blood stream, and result in an acute inflammatory reaction, or that ecologic relationships are later due to lowered resistance allowing development of an inflammatory process in the lower genito- urinary tract.

Other factors may be: direct trauma either mechanical or chemical, and antibiotics, especially penicillin, which are so widely used in both venereal and non-venereal diseases.

Bacterial organisms have received more attention as suspected aetiological agents, than other microbiological

organisms, because of the numerous inflammatory diseases, which they are known to cause, and their constant presence in our environment.

Essentially every recognised species of so-called "pathogenic" and "non-pathogenic" bacteria has been isolated from the urethra, both diseased and normal, but no pattern of flora has emerged, as being unique to the exudates of a bacterial urethritis.

The term "Abacterial" appears to have different connotations to different authors, but generally speaking there are two:

1) no bacteria found in stained smear of the exudate and/or negative culture, and

2) no "pathogenic" bacteria noted on a stained smear or isolated by culture.

The following have variously been regarded as possibly responsible for the bulk of cases of Abacterial Urethritis:

1) Trichomonads (29,30,31,32,33,34)
2) Spirochaetes (35)
3) Pleuropneumonia-like organisms (P.P.L.O) (36-67), (113-117) relatively "Mycoplasma Species"; (the last named, established recently, seems to be the most proper one according to the terminology introduced by Freundt 1955, Edward 1955, and Edward and Freundt 1956 (68)).
4) Viruses (69-73)
5) Bacteria especially in their "L-form" (74-80)

In my series all cases of Urethritis, in which even a few bacteria have been found in the smears, have been

excluded from this group of Abacterial Urethritis. Smears, always taken with the usual precautions, were repeated several times on consecutive days. If other organisms were found in stained smears, even in small quantities, the cases were diagnosed as bacterial urethritis, and excluded from this series.

Different authors from various countries give the percentage of Abacterial Urethritis of venereal origin as between 40-80% of all cases of urethritis. Harkness for example gives 73.5%, Grenley - 42.8%, But there are other workers such as Weckstein, Rasmussen, Hughes and Carpenter, who report all their cases to be bacterial.

In my series there were one hundred and three cases of Abacterial Urethritis, and the clinical findings (and percentages) of the disease are assessed on this figure; 21 of the cases, however, defaulted either during treatment, or before completion of the period of duration. The figures for the results of treatment are, therefore, based on the 82 cases, who completed the period of observation up to the test of cure! This group was seen and treated by me during the 3 years 1953-56. (The total number of such cases reported in Glasgow in two venereal disease clinics during the period 1954/6 was 491 cases). There is still some difference of opinion amongst the local specialists, as to what constitutes the diagnosis of Abacterial Urethritis - depending apparently on the presence of smaller or larger numbers of saprophytes or commensals in the urethral smears. My own position has been made quite clear above.

In the series seen, there were 31 cases (37.8%) of the Hecht type, and 51 cases (62.2%) of Waelsh type

of urethritis. There were 17 cases (20.7%) having some atypical symptoms as e.g. short incubation period and very mild urethral discharge, or long incubation period with profuse discharge, with very mild, or the complete absence of pain. These cases being just between the two typical groups - intermediate types-were attached to one or other of them - (Hecht and Waelsh) to avoid a further arbitrary classification.

The primary acute "Abacterial Urethritis" of venereal origin known as Hecht Urethritis, is characterised by a short incubation period of 1 -3 days, profuse urethral discharge, and severe pain on micturition. The urethral discharge is usually muco-purulent. (scanty in some cases), but in the bulk of cases was frankly purulent, and clinically indistinguishable from that of acute gonorrhoea. The meatus is red and inflamed with occasional prolapse of mucous membrane. The urine in the first glass is hazy or muddy, the second glass with only a few exceptions is almost clear.

The second sub-group of 51 cases belongs to Waelsh Urethritis. Waelsh in his original description (1904) suggested, that the disease be called "Chronic Non-Gonococcal Urethritis". The disease is chronic or sub-acute in the first place, but it is a "primary" urethritis, therefore, name chosen by Harkness i.e. "primary sub-acute abacterial urethritis", seems to be appropriate. The disease is venereal in origin, and usually contracted from women with vaginitis or cervicitis. The primary lesion in women may be difficult to detect, only a very mild cervical secretion may be seen at the external os, yet it can be highly infectious. Waelsh in 1916 described 3 cases in which

the disease had been contracted from the same woman, and confirmation of similar instances is given by Harkness[2] 1950. The disease may be also contracted by sodomy. The incubation period in Waelsh Urethritis is as a rule very long - up to 30 days and over. In my cases the incubation period varied between 10 days and 28 days approximately, most occurred between 10 - 18 days. The long incubation attributed to this type of infection may be, because, the mildness of the early symptoms make it so easy to overlook. Pain on micturition was found only in these 8 cases, and was never severe. The urethral discharge was only in 4 cases, purulent, occasionally muco-purulent, in the bulk of the cases clear and scanty. Mucous membrane of the external urinary meatus only in few cases was red and inflamed. The urine in the first glass in 17 cases was hazy with light or heavy threads, the second glass showed some cloudiness only in 2 cases, the rest of the cases had had urine clear in both glasses, with the threads in the first one.

The aetiological data concerning these 82 patients are given in the accompanying table. (overleaf).

Feature		31 Cases of Hecht type.	51 Cases of Waelsh type.
Marital state -	Single	18	26
	Married	7	13
	Widowers or Separated	6	12
Age -	Range	18-43	17-52
	Average	27	31
Occupation -			
	"White-collar"	17	36
	Manual	14	15
Previous History-	Gonorrhoea	7(22.5%)	11(21.5%)
	Syphilis	1	2
	Urethritis		7
Previously treated with penicillin for various causes		19(61.3%)	22(43.1%)
Complications -			
	Posterior Urethritis	6	
	Acute Prostatitis	1	
	Epididymitis	3	
			2(both admitted alcohol and sexual intercourse whilst urethritis active.

Methods of Examination

The following investigations were performed in each case of this group:

A. Gram stains for organisms

B. Dark-ground examination for Trichomonas (Leptospirilla).

C. Giemsa and Fuelgen stains for inclusion bodies

D. Cultures for any growth (and Trichomonas)

E. Cultures (special media) for P.P.L.O.
F. Prostatic smears
G. Urine (acidity or alkalinity)
H. Urethroscopy - Harrison (in 16 cases, 7 - Hecht, - 9 Waelsh sub-group)
I. Urethroscopy - Swift-Joly and scrapings in some cases "experimenti causa".

After these investigations were completed treatment was begun.

A. Gram stains. It must be noted that in this group of 82 cases with Abacterial Urethritis, the patients were specially selected. If two slides of the urethral discharge (in each case) stained with Gram revealed only pus cells and epithelial cells, then the case was classified as typical Abacterial Urethritis. In those cases in which even a few other organisms have been found in two or sometimes several slides stained with Gram, such cases were excluded from this group. It must be reiterated that the usual precaution and attention was always paid to cleansing the external meatus of the urethra, and to collecting the specimens. Therefore, Gram staining had in this series a considerable diagnostic vaule. The eighty-two cases were purely abacterial, the specimens contained only pus cells (abundant or scanty), and epithelial cells. All defaulters as already noted, were excluded from that group.

B. Dark-ground for Trichomonas (and Leptospirilla).

Dark-ground examination revealed trichomonas vaginalis in 3 cases (3.6%).

First case - a man, 46 years of age, married, labourer (no extra marital intercourse), was seen in April 1954. He stated that he had previously had several similar

attacks of urethral discharge, which appeared suddenly, and after several days up to several weeks, disappeared spontaneously. The present urethritis appeared about 9 days after sexual intercourse: the discharge was milky, more liquid than in gonorrhoea, Gram stained slides revealed only pus cells and epithelial cells. Dark Ground was negative, urine in first glass was clear with threads, in second glass clear. The patient admitted that his wife was attending for some time a female V.D. clinic. It was found, that she was suffering from trichomonas vaginalis. On the next visit (the patient kept urine in the bladder for several hours) dark ground revealed in first specimen, trichomonas vaginalis.

The second case - a man, 28 years of age, single, was seen in November 1956. He developed urethral discharge two weeks after casual sexual intercourse. He had had gonorrhoea three years before, and was treated with penicillin. He complained of burning sensation and painful micturition. On examination there was a small but purulent discharge (clinically indistinguishable from gonorrhoea). Gram stained slides revealed only pus cells and epithelial cells. The urine was slightly hazy with threads in the first glass, and clear in the second. Dark ground revealed trichomonas in first specimen.

The third case - a man, 35 years of age, single, a sailor, was seen in December 1956. On board ship he was treated with 60 tablets (probably sulphonamides) by his superior officer, for a urethral discharge, which appeared on 8th day after sexual intercourse in one of the Spanish ports. The discharge diminished greatly, but never disappeared completely. There was no history

of venereal diseases in the past. He was seen in the clinic on the 9th day after completion of the treatment. The patient did not complain in general, only the continual discharge worried him. On examination there was fairly abundant milky discharge, urine was clear, with tiny light threads in the first glass. Gram stained specimen showed only multiple pus cells and scanty epithelial cells. Dark ground for Trichomonas was positive on third successive examination.

In each of these cases the diagnosis of Trichomonas Vaginalis was based on the motility of Trichomonas and its flagella. In all three cases cultures (specimens inserted into the carrier Stuart media), gave negative results, even with several repetitions. In case 1 and 2 the cultures were completely negative, in case No. 3 the culture growth consisted of staphylococcus albus (very scanty growth). All three cases were treated with Acetarsol (1gm. daily - four times a week for four weeks). In the first case the discharge ceased almost completely on the second day of the treatment. It has to be borne in mind that this may have been a spontaneous recovery, which happens so often in this kind of urethritis. In the other two cases the discharge disappeared at the completion of the treatment but in Case No. 3 reappeared eighteen days later, although Trichomonas has not been found on several occasions. Chloromycetin capsules cleared this urethritis. The test of cure about three months since the disappearance of the clinical symptoms in all patients became negative. There were no complications during the treatment.

In three out of 82 cases Trichomonas Vaginalis was found under dark-ground examination. Diagnosis grounded

on motility and flagella. Cultures in all three cases were negative. It must be mentioned that in other genuine cases of N.G.U. (bacterial and abacterial) about 200 cases altogether, cultures were always performed, and were negative for Trichomonas. In all cases of acute gonorrhoea treated with penicillin, in which the discharge remained one week after the treatment (post gonococcal urethritis), cultures for Trichomonas were also performed but gave negative results.

My results are similar to those of other workers - Lydon[31]. The very high percentage obtained by Coutts et al [30](68%) can be explained rather by the geographical situation (Chile). Almost all European workers state, that Trichomonas Vaginalis in the male is one of the causes of N.G.U., but their figures are not higher than 3 - 10%. Pierre Durel and Andre Biboulet,[82] Cl.Sorel[29], Willcox[74], Harkness[2], Whittington[33], Bourne.[34]

Different workers have different approaches concerning the search for Trichomonas: some prefer the traditional (classical) method by direct examination between slide and coverslip, some the method of staining with May Grünwald Giemsa, and others dark ground examination or culture method. Whatever the method employed, it is useless to make a search if the subject has urinated; it is exceptional to detect it under such conditions and it is essential to take the specimen in the morning, before the first micturition. For this purpose two slides may be given to the patient, explaining to him, how to obtain the specimen, and warning him above all <u>not to stick</u> the two slides together before they are dry, since this makes the preparations unusable. But it is also essential to make sure of patient's nocturnal micturition. In such situation retention of urine for 5 - 6 hours is usually satisfactory for investigation,

especially, that bulk of the patients prefer and can attend the clinics in afternoon or at night only.

C. Giemsa and Fuelgen stains - for Inclusion Bodies.

It has been customary to designate as "inclusion bodies" any atypical structures seen within cells, believed to be infected with a virus. Consequently the inclusion bodies are a miscellaneous assortment of intra-cellular formations of varying nature and significance. Some, as the "Negri bodies" of rabies and the "Bollinger bodies" of fowl-pox, are sufficiently characteristic to be of diagnostic value. Others do not differ in any essential respect from structures occasionally seen in cells, when no virus is present. As Ludford(95) has pointed out "there has been an unfortunate tendency to study infected cells cytologically, without a preliminary study of the morphological changes, which occur in the same cells during autolysis, in the absence of micro-organisms".

The commonest form of intra-cellular inclusion is a rounded body, larger than the nucleolus, which stains intensely with acid dyes (such as eosin), and sometimes occupies almost the entire nucleous. Such bodies have been variously interpreted as accumulations of virus particles embedded in a matrix, or as the result of the reaction of the cell to the presence of the virus. Without confirmatory evidence, it is unjustifiable to accept the presence of acidophil intranuclear inclusions alone, as proof of virus action. This matter will be discussed later in connection with the use of different stains.

In 1910 Lindner(69) drew attention to the presence of intracytoplasmic inclusions observed in the urethral

cells of subjects suffering from urethritis. Comparisons were made between these formations and those, which had been described by Stargardt and then by Schneichler (1909) in the conjunctival cells of new born babies, suffering from amicrobial ophthalmia. One of the aetiological agents of the complaint was discovered, namely - Chlamydozoon Oculogenitale. This infective agent is believed to occur also in inclusion cervicitis. This is shown by the large number of cases reported in the literature (Harkness),(2) in which infections have been passed from one person to another, and more particularly by the passage of infection from women to men, during sexual intercourse immediately before or after a menstrual period. It is passed from women to babies during the passage of the head through the infected genital tract of the mother. It must also be noted that inclusion conjunctivitis (Blenorrhoea) in adults, and sometimes urethritis, may be contracted in swimming baths containing the virus ("swimming bath" conjunctivitis). This has reached the water either from the genital tract of the female or, more probably, from urination by both sexes, whilst bathing. Still further evidence is provided by the morphological identity of the viruses in the three conditions: inclusion urethritis, inclusion cervicitis and inclusion conjunctivitis. Since 1910 (Lindner) innoculation experiments have been performed by many workers in both human beings and animals. Fritsch, Hofstätter and Lindner inoculated the urethral discharge of a man suffering from Waelsh urethritis into the conjunctivae of a monkey. Wolfrum (1910), Gebb(1914), Taborisky (1930), Thygeson (1934), succeeded in transferring by inoculation, inclusion conjunctivitis to human beings. Thygeson and Mengert (1936) infected the other eye in cases with unilateral involvement.

Aust (1920), James (1930) and Thygeson (1934) showed, that mothers with inclusion cervicitis, may infect their own eyes with the virus, but Harkness[2] p. 57 is of the opinion that these infections may well have been blood-born (as are conjunctivitis and arthritis associated with Reiter's syndrome). Julianelle and his collaborators (1936) showed that the genital and conjunctival secretions retained their infectivity for both men and animals, after passage through bacterial filters. In 1929 Hellerström attributed certain forms of urethritis of the virus of Nicolas-Favre disease.

Since 1940 an increasing amount of work has been done in this field, to which a noteworthy contribution has been made by the outstanding research carried out by Klieneberger- Nobel[36,38,39,41-43,48,49,52,55,57,67,77] in England, by Dienes[44,46,64,75,76,79] in U,S.A. and by Tulasne[80] in France. Harkness[2,22-24,78,99] in England, and Durel and co-workers[72,82] in France have dealt with the clinical and therapeutic aspects of these complaints. Moustardier, Bryson[69] and Perrey have on several occasions reported the results of their bacteriological and clinical studies.

Urethritis caused by Chlamydozoon.

The name "Chlamydozoon" was endowed by von Prowazek. This worker in 1907 considered the inclusion body to be composed of a mass of small virus particles, which he called elementary bodies, surrounded by a mantle of amorphous material produced by the cell in reaction to the virus. On this basis he suggested that viruses should be called "Chlamydozoa" or "cloak animals".

The virus (chlamydozoon oculo-genitale) belongs to the order Rickettsiales and is morphologically

indistinguishable from that of Trachoma and the Lymphogranuloma - Psittacosis - Pneumonitis group. It consists of elementary and initial bodies, which show up well in Giemsa-stained scrapings of conjunctiva, cervix and urethra.

It should be remembered, however, that inclusion bodies are more easily demonstrated in scrapings from the conjunctiva and cervix, than from the urethra. This, in all probability, is due to the difficulty in taking adequate specimens from so sensitive a structure as the urethral mucosa.

The elementary bodies, 233 micro/u in size (Thygeson 1934) are seen either in the cytoplasm of epithelial cells (often arranged in a "crescent" around the nucleolus) or lying free in the exudate between the cells. Mature inclusions are made up almost entirely of elementary bodies. The initial bodies (First described by Lindner 1910) are larger in size and are seen most frequently in young inclusions; they are either alone or in association with elementary bodies and occasionally lying free. An elementary body after infecting a cell gives rise to an initial body, that develops into a small cluster of initial bodies. These appear as red or purple bodies sometimes in a pale blue staining halo, lying free in the cytoplasm of the epithelial cell. However, a large homogeneous body sometimes results, which may be of sufficient size to distort the nucleolus. Subsequently small granules appear in this body, giving rise to a typical colony. The smaller and more common type of initial body appears to undergo repeated division, which results in a small colony of elementary bodies.

The spheroidal granules in these inclusions are identical, but minute differences in size may be detected in the granules of separate colonies. Further increase in size gives rise to inclusions of two types. One is spheroidal body often indenting the nucleolus by its pressure, the other is a crescent-shaped body lying with its concavity towards the nucleolus. These types of inclusions are determined by the position in the cell in which the initial body has settled if lying free in the cytoplasm a spheroidal colony results; if adjacent to the nucleolus the body is crescent-shaped. Continued enlargement results in a cell, the cytoplasm of which is packed with elementary bodies. Rupture of these mature inclusions sets free large numbers of elementary bodies to infect the cytoplasm of other epithelial cells, thereby, completing the developmental cycle. Of course it is very rare for all these forms to be found in one urethral scraping; closely related types are more frequently found together.

Chlamydozoon cannot be cultured. Attempts made at cultivation on the fertilised egg have so far given uncertain results.

Consequently the diagnosis of such forms of urethritis is based only on direct examination of the smears stained with Giemsa technique. Care must be exercised in interpreting inclusions merely on their staining characteristics. The earlier workers, including Lindner, relied more on morphology than staining reactions and, unlike many of the modern virus experts, they were not afraid to accept the red granules as virus.

Some artefacts and products of cellular decomposition bear a striking resemblance to virus (or pleuropneumonia-like) inclusions, and to the constancy, with which they are found. It may well be, that they represent a phase of development so far unrecognised. They are:-

a) intracytoplasmic vesicles, which when sufficiently large, may indent the nucleolus. They contain red or purple staining granules of comparable size, but these are sparse.

b) numerous bodies found scattered throughout the cytoplasm or stuffing the cell. These bodies are larger than the granules described under virus inclusions, and their size shows marked variation; some are large as the small virus colonies, but they are homogeneous and more basophilic, in some cells the nucleolus is pyknotic. Here the doubtful inclusions are probably due to decomposition of the nucleolus. In most of them, however, the cell appears perfectly healthy.

c) granules due to ruptured polymorphonuclear cells.

d) erythrocytes may give also rise to confusion, not only "in vivo" but also "in vitro" preparations when whole blood has been used in the composition of the medium. They appear as characteristic morula-like bodies, containing purple Rickettsia-like structures against a blue matrix. The aggregations of pleuropneumonia-like organisms do not show this background. The Rickettsia-like structures are often arranged

at the periphery of the morula, and may show marked bipolar staining. The morula bodies are probably formed by fragmentation of siderocytes, and in urethral smears transitional forms between these bodies and erythrocytes may be found, although, the morula-like predominate.

In one hundred and three cases (including 21 defaulters) Giemsa stained (prolonged) and Fuelgen examinations were done. In each case at least two slides were prepared for each stain, in some cases even more.

Technique of taking Urethral Scrapings.

A very careful cleansing of the meatus and fossa navicularis with spirit is essential, then a rigid platinum loop is passed two inches down the urethra, and withdrawn with a quick movement. In some cases material from the urethra was taken by using a modified urethroscope of the Swift-Joly type. Smears were prepared from the scrapings and immediately fixed in acetone-free methylalcohol for three minutes, and stained with Giemsa (1/10) for 24 hours. A second preparation was stained by the Fuelgen-Schiff, method.

I would stress again the difficulty in finding cells with inclusions. I am rather disturbed by the fact, that even in proven cases only one or two epithelial cells, in the whole slide, contain inclusion bodies; whilst in other diseases from the group of "Psittacosis" inclusion bodies are very numerous. Before considering the findings as positive, I tried to make quite sure about the appearance of the inclusions. In a positive smear

there must be a distinct nucleolus and cell boundaries, corpuscles stained a definite violet-purple with Giemsa, granules of regular size in a clearly delimited crescent-shaped group, and the slide without too much cellular debris. All slides with even a few micro-organisms were eliminated from investigations for inclusions.

This is perhaps the reason, why my percentages are lower than certain other investigators. If cells which are merely doubtful are regarded as positive, then inclusions may be said to be present in one slide in every four or five. Typical inclusions, whose significance is unmistakeable, are confused with atypical ones without any aetiological value, and thus the whole position becomes uncertain.

In my series on one hundred and three prolonged Giemsa stained slides showed inclusion bodies in 11 cases of Waelsh Urethritis (10.6%), and 7 cases of Hecht Urethritis (6.8%)., i.e. in 103 cases there were 18 cases (17.4%) of positive inclusion body findings.

In the first sub group of eleven positive cases, in two cases a pair of initial bodies were lying free in the cytoplasm; in one case a pair of initial bodies were adjacent to the nucleolus. The eight remaining cases showed "crescents", early, small or fully developed, sometimes there were single crescents, in some cases even two or three in one field.

In the second sub group of seven positive findings, only one specimen showed a colony of elementary bodies slightly distorting the nucleolus, the remaining six

cases revealed "crescents" in various forms of their development.

From the sub group of eleven cases of Waelsh type of urethritis in which inclusion bodies were found, 5 cases had had gonorrhoea in the past, and had been treated with penicillin. Another two cases received penicillin in the past for other reasons, 4 cases had not received penicillin or other antibiotics in the past (their own statement which had to be accepted).

From the sub group of seven cases of Hecht type of urethritis in which inclusion bodies were found, 3 cases had had gonorrhoea in the past, and had been treated with penicillin. One case received penicillin in the past for some infective dermatitis, and only 3 cases stated, that they never had been treated with penicillin or other antibiotics.

It is striking what a large percentage in both sub groups (11 in 18 cases = 61.1%) had been treated previously with penicillin.

As stated above, urethral scrapings from each patient, at least one and in many cases two slides, were stained with Fuelgen, which shows up the thymonucleic acid in the nuclear structure. In all cases stained with Giemsa, which revealed negative findings for inclusion bodies, only two showed these with Fuelgen stain. The explanation of this might be in the technique of scraping and collecting specimens on the slides.

Fuelgen stained positive findings for inclusion bodies in previously positive findings with Giemsa stains are as follows:-

Waelsh Urethritis	Giemsa Stain	No.of cases +ve 11	% in 103 - 10.6%
" "	Fuelgen stain	" " 5	" " 4.8%
Hecht Urethritis	Giemsa stain	" " 7	" " 6.8%
" "	Fuelgen stain	" " 3	" " 2.9%

If we compare the positive findings of inclusion bodies with the Giemsa stain and Fuelgen stain percentage is:- Giemsa 17.4% (18/103), and Fuelgen 7.7% (8/103).

Fuelgen stain thus diminishes my numbers and my positive findings for inclusion bodies. The literature reveals that only very few workers have used Fuelgen stain in their researches. Giemsa stain is almost the only one mentioned by them, and their positive findings for inclusion bodies are, therefore, much higher.

I have also to confess, that mistakes and errors in my technique as well as my appraisement of genuine positive findings might bring my figures to a lower level.

I believe, that a more satisfactory technique should be developed for the correct interpretation of the

presence of the inclusion bodies seen in the urethral tissue of the patients with N.G.U. (Abacterial).

It is of importance to underline, that Fuelgen stained slides revealed in all positive cases inclusion bodies lying inside the cytoplasm or free outwith the cytoplasm, except in one case, in which a crescent-like shape was found. The inclusion bodies stained with Fuelgen appear as violet-purple granules; they are very regular in size and clearly delimited. It is very well known that Fuelgen stain does not stain any kind of micro-organisms.

By taking this into consideration, I can assume their viral origin with more certainty, than with the specimens stained with Giemsa.

It should be noted that scrapings performed with the modified Swift-Joly urethroscope - the full description of that method is given further on under par. "I" - revealed inclusion bodies in five of seven cases, in the rest of the cases specimens were collected by the rigid platinum loop.

<u>This experiment indicates that</u>:-

a) inclusion bodies are harboured not only in the vicinity of the fossa navicularis, but also in the further part of the anterior urethra.

b) <u>scrapings by the loop</u> are performed at random, and in patchy inflamed mucous membrane; it is very easy to miss the affected area, which should contain inclusion bodies.

c) <u>scrapings by the modified Swift-Joly</u> urethroscope allows us to collect specimens from any place,

especially from the suspicious area situated in the further part of the urethra, which is difficult or impossible to reach by the loop. The danger of the instrumentation of the inflamed urethra must always be kept in mind, and, therefore, not allow this method in each case; those, which have been performed by the Swift-Joly urethroscope were only done "experimenti causa".

It should be mentioned, that the specimens collected by the Swift-Joly urethroscope in 5 cases of Bacterial Urethritis did not differ from the scrapings collected by the platinum loop. Exactly the same micro-organisms were found on the slides, and in cultures in the same patients, when material was obtained by those two methods. Only one patient in 16 became slightly dizzy during this method of examination.

D. Cultures - for any growth (and Trichomonas).

As it was mentioned previously (Par.B) in 3 positive cases for Trichomonas Vaginalis diagnosed by Dark-Ground examination cultures (heated blood agar media for gonococci and other organisms) revealed negative results in 2 cases, in 1 case (cas No. 3) culture revealed staphylococcus albus (rather very scanty growth). In another 21 cases from this group of 82 cases (10 cases from the Hecht sub-group, and 11 cases from the Waelsh sub-group of urethritis) specimens were collected and inserted into the carrier Stuart media, and inoculated on the ordinary 10% chocolate agar media for growth and sensitivity tests.

In all these cases previous Gram stained slides revealed only pus cells and epithelial cells, and no sign

of other micro- organisms had been noticed. In spite of careful precautions to ensure the sterile collection of the specimens, (by swabs), seven of 21 specimens (33%) revealed on cultures different micro-organisms. They were as follow:

a). 2 cultures: only staphylococcus aureus (coagulase +ve)
b) 2 " : enterococci and few diphteroides
c) 1 " : diphtheroides and staphylococcus albus (coagulase -ve)
d) 2 " : mixed organisms, probably contaminants - mainly pigmented staphylococci and diphtheroides. (The staphylococci were all coagulase -ve).

ad a) - sensitive to : aureomycin, streptomycin and chloramphenicol-resistant to penicillin.
ad b) sensitive to : penicillin, aureomycin and chloramphenicol.
ad c) sensitive to : aureomycin, chloramphenicol and penicillin.
ad d) sensitive to : some to penicillin, aureomycin, streptomycin and chloramphenicol, others to: aureomycin, streptomycin and chloramphenicol, but only slightly to penicillin.

In only two cases did the laboratory label the organism as "probably contaminants". What explanation can be given for the other 5 cases in which microscopically only pus cells and epithelial cells, but no other organisms were found, although, cultures revealed organisms in abundance? Were they contaminants again ?.

All these five patients, who had not been treated up to this time, on next occasion were examined once again carefully. In one case the urethral discharge

disappeared completely on the ninth day since his first attendance. In another two patients scanty muco-purulent discharge revealed in Gram stained slides only pus cells and epithelial cells. Cultures were again prepared, and revealed in one case: negative results,"the second" culture showed very scanty diphtheroides and diagnosed by the laboratory authorities again as "probably contaminants".

The last two cases in Gram stained slides showed multiple staphylococci and diphtheroides, confirmed by cultures. These two patients assured me, that they did not have any fresh sexual intercourse, they did not drink, and both were married. They had had several recurrences of their urethritis, and they wanted to get rid of their disease at any cost. They were trustworthy.

It is again a question, that the organisms were in the "L-form", and, therefore, inaccessible for observation, when previous examinations were performed?. Giemsa stained slides in these 2 patients did not show any suspicion of inclusion bodies. In one of these cases the urethral discharge disappeared spontaneously on the sixteenth day of his first attendance, twenty-seven days since the discharge appeared, and forty-one days after the last sexual intercourse.

The second case had been treated at that time with sulphatriad tablets, two tablets, four times daily for 6 days. His urethral discharge disappeared completely on the fifth day of the treatment.

Prostatic gland investigations now done for the first time in both these cases revealed no abnormality.

The first case reported back to the clinic after 17 days, with a recurrent urethral discharge. The second case also had a recurrence 8 days later, having been symptom free for 23 days.

In both cases only pus cells and epithelial cells were found in repeated slides. Giemsa stained slides revealed in both cases inclusion bodies, but these were not confirmed by Fuelgen. Culture in one case was completely sterile, in the second case it showed, scattered staphylococci, which were diagnosed as "probably contaminants" by the laboratory authorities. Both received aureomycin capsules 250 mgm four times daily for 5 days, and became symptom free for another two months. The test of cure at that time did not show any abnormality. These patients have been real "enigmas" in my investigation. I do not think that frequent collection of the urethral smears and only one investigation during their illnesses of their prostatic glands could have any influence on the presence and appearance of the micro-organisms. They both started as typical cases of "Abacterial Urethritis", and then became bacterial, and finally reappeared as abacterial. They had not been previously urethroscopically examined. Some error in urethroscopy technique could introduce micro-organisms into the urethra, but they were not urethroscopically examined. Recent observations (Shackman and Messent),[96] suggest, that instrumentation does not materially affect the nature of the bacterial flora of the male urethra. It is also important to add, that cultures for P.P.L.O. performed during the second advent of the Abacterial Urethritis were negative in both cases, which is rather surprising. One should expect a positive culture for P.P.L.O.

E. Pleuropneumonia-like organisms (P.P.L.O.) Mycoplasma species, Mycoplasmata.

The organisms of the Pleuropneumonia Group (P.P.) are of particular interest (Edward[56] 1954) because, although, they have distinctive properties, they resemble in certain respects other widely different organisms. They can exist as particles of 150 micro/u in diameter i.e. about the same size as the elementary bodies of vaccinia virus, but are, nevertheless, capable of multiplication in cell-free media. Their relationship to bacteria has recently been complicated by the finding, that under unfavourable conditions many bacteria undergo variation to a so-called "L-phase", which morphologically and culturally may resemble an organism of the Pleuropneumonia Group.

Certain organisms from the P.P. group are the cause of some very serious diseases in animals, and have a practical significance for the veterinarians; e.g. contagious bovine pleuropneumonia is one of the most serious infections of cattle. In some parts of the world it causes much devastation even today, and is difficult to eradicate. The other strains have been incriminated as a cause of disease in man, but evidence for this is much less definite.

It was recognised by Pasteur, that contagious P.P. of cattle was caused by a specific infective agent, which would not be seen under the microscope, and did not grow in ordinary nutrient broth.

The first number of the groups of pleuropneumonia organisms was isolated in cell-free medium by Nocard and

Roux in 1898[2] from cases of pleuropneumonia of cattle, a disease in which the essential pathological lesions are: gross pulmonary oedema, pleural exudate and arthritis.

Bordet and also Borrel[56] 1910, first described its peculiar pleomorphic morphology, and named it "Asterococcus mycoides". It was filterable through a Berkefeled V filter, and Elford (1929)[56] using Gradocol filters, showed that cultures contained particles 125-150 micro/u in size. The organism was, therefore, regarded as a virus, and for nearly 25 years occupied an unique position amongst micro-organisms, because, although it had the dimensions of a virus, it was capable of multiplication in cell-free media.

In 1923 a similar type of organism was described by Bridré and Donatien,[2] and named as the cause of contagious agalactia of sheep and goats. The syndrome of agalactia includes: mastitis, arthritis, keratitis and vesiculo-pustular skin lesions. In 1933 Wroblewski[56] named these organisms "Anulomyces Agalaxiae".

Since then, the morphology and biochemical properties of P.P. organisms have been investigated and described by many workers: Holmes and Pirie 1932, Ledingham 1933, Klieneberger.[39,41,43,48,49,55,57] In 1934 Shoetensack isolated a similar organism from dogs suffering from distemper, and in the following years similar organisms from many different sources have been found. Because all these organisms resembled the organism of bovine pleuropneumonia they were named "Pleuropneumonia-like Organisms"(P.P.L.O.).

The characteristics of P.P.L.O. are as follows:

1) They do not stain with simple bacteriological stains, but can be demonstrated by prolonged staining with Giemsa.

2) They do not grow in ordinary media, but do grow rather feebly in rich media containing 10% to 40% of serum and produce a characteristic type of colony on surface cultures. The colonies measure only 1 - 2mm in diameter, and have a central boss and flattened periphery. Their morphology can be studied by Dark-Ground illumination or impression preparations.

3) They are very pleomorphic in form varying from minute "elementary bodies" and "spherules" to "asterodiscules" and "branching filaments".

4) They are filterable, although, with considerable reduction in numbers, through Gradocol membrane down to about 0.4u. in average pore diameter.

Harkness[2] quoting Turner (1935) states, that there are at least five morphological stages in their development - namely: granular, filamentous, ramification, chain formation, and disintegration. The small filter passing granules or elementary bodies, considered to be the spore stage are referred to by Turner as "conidioids", and measure 0.2 - 0.4.u. in diameter. They are coccoid, diplococcoid or cocco-bacillary forms, all of which stain well with Giemsa. The granular bodies develop into larger spheroidal bodies (0.4 - 0.8.u. in diameter), following which one or more spherical nodes appear on the periphery. These nodes or buds grow from the spheroid, but remain attached to it by a short filamentous thread, although, examination of fresh strains also shows long, poorly staining filaments. According to Topley and Wilson,[25] the stage of ramification consists of a tangled, branching mycelium. In the stage of chain formation the

mycelium divides and simulates a chain of streptococci. Disintegration completes the cycle with the breaking up the chains into multiple granules, coccoid, diplococcoid and cocco-bacillary bodies.

Topley and Wilson state, that Pleuropneumonia-like Organisms do not give rise to inclusions in the tissues. (The connective tissue of the lungs is distended with yellow fluid containing large numbers of the bodies seen in culture).

In 1935 Klieneberger[36,38,42] isolated another strain in cultures from rats and mice, infected with "strepto-bacillus moniliformis", and named it "L1". Klieneberger[77] herself considered the "L1" organism the symbiont associated with the bacillus, but in 1949 she agreed with Dienes,[76] that it was only a variant of the bacillus. Since then a number of organisms of the same group, usually referred as Pleuropneumonia- like Organisms (P.P.L.O.) or "L - organisms" have been described, which cause: arthritis, abscesses, pneumonia, rolling disease (Findlay)[50] and other complaints chiefly in animals: cattle, sheep, goats, dogs, rats, mice and birds.

Laidlaw and Elford in 1936[51] have also isolated free living strains from sewage. These strains differ from those isolated from animals by their ability to grow on simpler media without enrichment with serum, and also by their lack of pathogenicity for animals. Seiffert in 1937[2] also isolated them from soil and manure.

In the last twenty years organisms of both groups have been identified in the urogenital tract of men and women. Dienes and Edsall 1937[79] isolated from a

Bartholin abscess of a laboratory worker a strain, which was possibly human, although the infection at the time was considered to be due to the patient's contact with rats. Dienes in 1940,[44] however, was really the first to record the presence of Pleuropneumonia-like Organisms in the cervical secretions of females, the majority of whom were suffering from pelvic gonococcal infections.

While in 1934 only two members of the group were known, the progress of discovery of P.P.L.O., from 1941 has been very rapid. It was discovered, that widely dispersed in nature, there was a group of organisms of numerous species, some pathogenic, some saprophytic, which had unique properties, distinguishing them from bacteria, rickettsiae and viruses. Sabin 1941.[40]

Smith 1942[45] was the first to isolate these organisms from the urethral discharge of a male with Non-Gonococcal Urethritis and arthritis.

Dienes and Smith 1942[46] recovered Pleuropneumonia-like Organisms from the cervical (23 of 77), and vaginal secretion of females (1 of 8), and from the prostatic secretion (3 of 36), and urethral discharges in males (1 of 8).

Beveridge 1943[47] demonstrated the presence of Pleuropneumonia-like Organisms in 4 of 24 cases of Non-Gonococcal Urethritis in the male.

Harkness 1945[78] in an address to the Medical Society for the Study of Venereal Diseases in 1944, reported the frequent finding of inclusion bodies, possibly due to a virus in the urethral discharge of primary uncomplicated Non-Gonococcal Urethritis.

Klieneberger Nobel in 1945[52] cultured "L" organisms from 18 of 45 cases with vaginal discharge.

Johnston and McEvin 1945 reported two cases of Non-Gonococcal Urethritis, in which "L" organisms were isolated, and in which inclusion bodies cocco-bacillary basophilic elementary bodies were demonstrated in the cytoplasms of the epithelial cells in the urethral discharge.

Salaman in 1946[53] demonstrated colonies resembling those of "L" organisms, from what was considered to be pure cultures of gonococci. These organisms were obtained in 34% of men and 61% of women suffering from gonorrhoea. He obtained them, however, in only 7% of men with Non-Gonococcal Urethritis. He also isolated them in 8% of prostato-vesicular secretions, and in 6% of men with residual Non-Gonococcal Urethritis, following successful sulphonamide or penicillin therapy for acute gonorrhoea.

Beveridge in 1943[47] and Beveridge and co-workers in 1946[56] isolated "L" organisms in 20% of Non-Gonococcal Urethritis in the male, and 27% in females with cervical erosions from whom men had contracted the disease.

Ruiter and Wentholt in 1950[37] isolated a P.P.L.O. in primary fusospirochaetal gangrene of the penis, and the same workers in 1953[58,59] isolated a new strain of P.P.L.O. in a case of fusospirillary vulvovaginitis, and named it "G strain".

In Non-Gonococcal Urethritis the incidence of P.P.L.O. reported by various workers varied from 7 - 53%. The following table according to Freundt,[68] shows the percentage of P.P.L.O. found by various authors in N.G.U. These figures are compared with the percentage of P.P.L.O. in gonorrhoea.

Percentage of P.P.L.O. in N.G.U. and GU. found by various authors.

Author	Year	Percentage in N.G.U.	Percentage in GU.
Beveridge	1943	17	-
Beveridge, Campbell and Lind.	1946	20	-
Salaman	1946	7	34
Harkness	1950	17	17
Melén and Linnros	1952	18	3
Nicol and Edward	1953	26	11
Wagner Morse and Kuhns	1953	12	-
Jensen	1954	22	-
Durel	1954	14	-
Shepard	1954	53	-
Freundt	1956	30	34

P.P.L.O. have also been isolated from the healthy male urethra in a fairly large number of cases, and also cultures of specimens from the female genito-urinary organs are very often positive. The results are even more conflicting than in N.G.U. and gonorrhoea.

Beveridge (1946) and Harkness and Henderson Begg (1948) failed to isolate P.P.L.O. from 67 and 50 normal controls respectively. However, positive findings

ranging from 10 - 36% were reported by: Salaman (1946), Dienes (1948), Melen and Linnros (1952), Nicol and Edward (1953), and by Durel and others (1954). Shepard (1954) in three population groups with different sexual activity found, 56% 33% and 2% positive cultures and finally Freundt in (1956)[68] found 53.6% of normal healthy adults had positive cultures.

Classification and nomenclature.

The first organisms of the P.P. Group to be isolated were given names; the organism of bovine P.P. in fact received at least four different names, each based on a different morphological interpretation of the nature of the organism. Symbols were later used to designate the numerous strains, mostly isolated from rodents, and identified by their pathogenic and antigenic properties. Sabin (1941a), who considered that organisms of the P.P. group differed fundamentally from bacteria, particularly in their method of reproduction, attempted a comprehensive classification, in which scientific names were given to all the recognised species. But it was not accepted, however, by the majority of the workers in this field. He, therefore, assigned them to a new class "Paramycetes", alongside the"Schizomycetes". The whole group was included in one order "Anulomycetales", which in turn was divided in two families, one containing species isolated from animals, and the other containing the saprophytic strains. The different species were grouped together into genera according to their animal host.

Previously Ledingham (1933) had suggested putting the two species known at that time into a new genus to be set up in the existing family of "Actinomycetaceae".

A third suggestion was to assign them to a new order "Borrelomycetales" (Turner) 1935a).

Thus the proposals made for classifying the organisms varied from placing them in a new genus of an existing family of bacteria to separating them completely from bacteria, and placing them into a new class. Dienes and Weinberger (1951) believed, that the various strains had been derived in the course of evolution from different bacteria, and suggested that the organisms belonged to a morphological group of miscellaneous origin, somewhat analogous to the "Fungi Imperfecti", and should, therefore, not be assigned to one order or family in a natural system.

Agreement on classifications and nomenclature can be reached only after deciding the relationship of these organisms to bacteria, including the "L-phase" variants of bacteria. The establishment of a proper nomenclature should not be delayed, as a breviation of P.P.L.O. cannot be translated from English into other languages. Moreover, the use of this term draws an unnecessary distinction between the organism of bovine P.P. and other species of the group. The term "L-organism" is sometimes used, because Klieneberger-Nobel named some of her original strains "L1", "L2" and "L3" etc. Although, this has the advantage of brevity, it should be avoided, as it refers only to a provisional system of labelling of strains by one worker. This system has also led to considerable confusion, because, the "L1" organism is now recognised to be a variant of a bacillus (streptobacillus moniliformis), whereas "L3", "L4", and "L5" of Klieneberger-Nobel were members of the P.P. group proper and isolated directly from animals.

Klieneberger-Nobel (1947) later called P.P.-like variants of other bacteria "L1-cultures". Other workers omitted the "one" and spoke of "L-type cultures" and, "L-forms" (Dienes 1948, Tulasne 1951). The prefix "L" has thus come to be associated with these variants and in the opinion of Edward[56] it should be restricted to them. There will be no suggestion then that, for instance, the "L3 organism" or the organism of bovine P.P. are variants of bacteria. Confusion has also arisen because "L-form" and "L-body" have been used to describe morphological changes in bacterial cultures, even when attempts to sub-culture a P.P.-like L-phase variant have failed. The changes to "L-forms" or "L-bodies" may represent "L-phase" variation, but on the other hand they may be simply degenerative changes.

There are two sub-divisions of the P.P. group; one contains strains believed to be saprophytic and capable of growing at 22°C. and on a simple media, and the other contains strains, which will not grow at 22°C., and which require media enriched with serum or ascitic fluid for growth. There are a number of species with different pathogenic and biochemical properties, each distinct antigenically. The organism of bovine P.P. is the type species; it was called "Asterococcus mycoides" by Borrel and his colleagues in 1910, and the rules of priority would appear to make the name valid. The choice of Sabin (1941b) of "Anulomyces agalaxiae" (the organism of contagious agalactia) as the type species from which to build a system of nomenclature, was perhaps unfortunate in that its properties have been much less studied. Moreover, the organism of bovine P.P. the first to be isolated, has already given its name to the group.

Ruiter and Wentholt (1952)[58] isolated P.P.L.O. from patients with ulcerative lesions of the glans penis; they were associated with fusiform bacilli and other bacteria, and the species was named the "G - strain".

Nicol and Edward (1953)[61] gave the names "Human type 1 and 2" to some species of the P.P. group due to their biochemical properties, and Edward in 1954[56] the name "Human type 3" to some other species. Freundt (1955), Edward (1955) and Edward and Freundt (1956)[68] introduced a new term for the P.P.L.O. namely: "Mycoplasma species" or Mycoplasmata". Recently, the name "Mycoplasma hominis" has been proposed by these two authors for types 1 and 2, and "Mycoplasma fermentans" for type 3.

Relationship of P.P.L.O. to the "L-form" (L-phase) variants of bacteria.

Very detailed general reviews have recently been devoted to the organisms of the "L-form" (L-phase) of bacteria. Knowledge of the "L-form" of bacteria is necessary to compare organisms of the P.P. type. The "L-forms" appear in culture media either spontaneously or when the bacteria are subjected to conditions unfavourable to normal growth and reproduction. The "L-forms" are variants of bacteria, which may be either stable or unstable. They no longer show the usual bacterial structure, but are pleomorphic, appearing in various shapes including rings, spheres, filaments and small filterable granules 175-200 millimicrons in size. They are able to grow on artificial media, and on solid media give characteristic colonies resembling those of the P.P.L.O.

According to Tulasne[80] there are two types of colonies: the "A" colonies, varying in size from 10 to 600 millimicrons, and the "B" colonies, which may be much larger. Although it seems to have been possible to transform a large number of bacterial species into "L-forms", and it may be that this variant exixts with all species, nevertheless, the experimental production of such forms is usually very difficult.

At present the transformation can be regularly produced with: Proteus, Vibrio, Staphylococcus fecalis, Achromobacter alcaligenes, certain species from Salmonella group and other Gram negative bacilli.

It is remarkable, that the passage of bacteria in a living organism as pathogenic agents and sometimes even as saprophytes (provided that the time spent in the organism is long enough), seems to sensitise the strains and to prepare them to a certain extent for the "L" transformation. This observation wuuld seem to imply, that a certain number of bacterial cells, either normally or under the effect of treatment with certain antibiotics, are present in the body in a state of equilibrium between the usual and the "L-forms". The complex process, which leads bacteria of the usual type to produce "L-forms" is called the "L-cycle" and is roughly as follows: when bacteria are placed in conditions capable of producing "L-forms" part of them die, become lysed and disappear. Each of the remaining living bacteria becomes transformed by a complex process into approximately circular giant forms 10 - 50 microns in diameter. Some of these are empty and look like rings, others contain very fine granules at the limit of visibility, about 200 millimicrons situated either in a viscid cytoplasm or in vacuoles formed within the giant forms.

The giant forms are pliable and can appear in a very large number of shapes; they are very fragile and have no rigid membrane. The giant forms break, open, and set free the granules which they contain. These granules, which are also pliable with no rigid enveloping membrane, represent the dwarf forms of the bacteria. If circumstances permit, each of the dwarf forms can give rise to further giant forms, and so the cycle can continue indefinitely. The agglomeration of dwarf forms, giant forms, forms intermediate between these two extremes and filamentous forms, constitute the "L colonies", which can be found in one of two types:

The "A" type colonies have on average a small diameter of 20 - 50 microns and greatly resemble both macroscopically and microscopically the P.P.L.O. colonies. If, after a certain number of passages on media unfavourable to the growth of normal bacteria, these colonies are sub-cultured on a medium adapted to the culture of P.P.L.O. only and favourable for them, they no longer reproduce the original bacterial forms, but develop indefinitely in their new form. These dwarf variants are stabilised, usually permanently, and they differ only occasionally in some few points of detail, from the P.P.L.O. colonies.

The "B" type colonies on the contrary differ rather sharply, especially in size, from the P.P.L.O. colonies. In general, they are larger (up to 2mm), more viscid, more raised above the surface and higher coloured. They can not always be sub-cultured in series on a medium identical to the one originally producing them. On the contrary, however, if they are sub-cultured on a medium from which the harmful agents bringing about the "L" transformation have been eliminated, they rapidly give rise,

even in a few hours to colonies of the normal bacterial type, with completely typical bacterial cells. Thus there is an automatic reversion to the usual type. It can be seen, therefore, that the distinction between the two types of colony is essential for comparison of the "L-forms" and the P.P.L.O.

Tulasne and Minck[80] mentioned another cycle of bacteria, which they termed the "M-cycle". The "M-cycle" occurs under the same conditions as the "L-cycle" but the final development of the elements involved is quite different. This cycle is as follows: normal bacteria when placed in bad cultural conditions, become transformed by a process analgous to that previously described in the giant forms. In the "M-cycle" the giant forms are generally without granules and do not produce dwarf forms. The giant forms can multiply for a certain time, but if the unfavourable conditions persist, they die and become lysed, and sometimes produce a very fine cellular debris, which occasionally may be mistaken for dwarf forms. These false dwarf forms are not viable and consequently can not be sub-cultured. If the giant forms are placed in a medium favourable to normal bacterial growth, they will divide and give rise to bacteria of the usual type. The "M" colonies are totally different from the "L-colonies". The former are much bigger, irregular in shape, often confluent and, above all have no distinct centre embedded in the medium. The three types of colonies "L-A", "L-B" and "M" may exist together in the same medium.

The "Ll" organism, the first "L-phase" variant isolated, was orginally regarded by Klieneberger (1935) as a P.P.L.O., which occurred as a symbiont in cultures of streptobacillus moniliformis. Tulasne (1951) believed that an "L-phase" especially in the stable form was

indistinguishable from an organism of the P.P. group. Dienes and Weinberger (1951) emphasised, that colonies of certain "L-phase" organisms may appear identical with those of true P.P.L.O. The similarities, however, between bacterial "L-phase" organisms and organisms of P.P. group may have been over-emphasised. Orskow (1942) described morphological differences between them. These differences were confirmed by Freundt (1950), who thought, that the "L-phase" organisms did not belong to the P.P. group. Edward[56] in his studies (1950b, 1953a) was of the opinion, that a culture can be identified as an "L-phase" organism, when it is examined at all stages of growth both macroscopically and microscopically. Further assistance can be provided by cultures in fluid and semi-solid media. When repeatedly sub-cultured in penicillin-free media most "L-phase" organisms tend to revert to the bacillary phase, especially in fluid and semi-solid media.

The first few sub-cultures of an "L-phase" organism are difficult and often unsuccessful, whereas those of an organism of the P.P. group are usually easy on a suitable medium. Klieneberger-Nobel (1954)[57] also drew attention to these differences between "L-phase" variants of bacteria and organisms of P.P. group proper, and claimed that they can be distinguished from each other.

The demonstration, that bacteria can exist in an "L-phase" led to speculation about the nature of those P.P.L.O., which exist independently of bacteria. Tulasne (1951) believed, that organisms of P.P. group were "des formes L des bacteries fixées et adaptées plus ou moins longtemps à un organisme vivant".

Although Dienes and Weinberger (1951) admitted the existance of an independent group of P.P.L.O., they suggested,

that the organisms had evolved in the past from bacteria changing to an "L-phase", which had become stable and persistent. They thought, that this change represented a simplification of structure.

An apparent similarity in growth requirements seemed at one time to support the notion, that organisms of the P.P. group need media enriched with serum or ascitic fluid, and so do the "L-phase" variants of Gram-ve bacteria. Subsequent investigation, however, has indicated an important difference in growth requirements between the two groups of organisms. Cholesterol or certain other sterols, appear to be necessary for the growth of organisms of the P.P. group, but not for the growth of "L-phased" organisms (Edward and Fitzgerald 1951b, Edward 1953a).

Edward[56] grew two "L-phase" organisms on a medium in which serum had been replaced by a serum albumin fraction plus an acetone insoluble lipid fraction of egg yolk, whereas the further addition of a cholesterol suspension to the medium was required to permit the growth of typical organisms of the P.P. group. If these findings are confirmed by observation on other "L-phase" organisms, they suggest a fundamental difference between the two groups of organisms. In 1950 Edward showed that some organisms of the P.P. group ferment carbohydrates, while others appear to lack this power. All the strains with fermentive capabilities tend to form acid from the same carbohydrates; all ferment glucose, maltose, dextrin, starch and glycogen, and some strains also ferment fructose, galactose and mannose. No strain was found capable of fermenting the other carbohydrates tested, including lactose, saccharose, mannitol and dulcitol (Edward 1950b).
This similarity in fermentation power suggests, that the

various organisms of the group are closely related to each other. In each group the species had been derived from a different bacterium, and was a stable and persistent form of "L-phase" variant. As Dienes and Weinberger suggested, the species might be expected to differ from each other in fermentative capabilities, because a bacterium in "L-phase" has been observed to ferment the same carbohydrates as it did in the bacillary phase.

This dispute among the many workers is still undecided. A few of them are still of the opinion, that there is a close relationship between the P.P. group and "L-forms", while the majority think, that the risk of confusing the "L-forms" with stable P.P.L.O. is non-existant.

The reasons they give are:-

1) Transformation is very rare.
2) Culture of"L-forms" is more difficult during the first sub-cultures than that of P.P.L.O.
3) At the onset the morphology of the "L-forms" is not exactly the same as that of the P.P.L.O.
4) In the absence of penicillin, the "L-forms" have a tendency to revert to their normal bacterial forms.
5) Bacteria having a biochemical action on the sugars retain it, at least in part, in the"L-forms" whereas, this activity with the human P.P.L.O. was never observed.

Pleuropneumonia-like organisms in Non-Gonococcal Urethritis (P.P.L.O. in N.G.U.)

The pathological significance of P.P.L.O. in N.G.U., although, only one of many problems concerning the aetiology of the latter condition, has been rather obscure until now. On account of the incomplete knowledge of human P.P.L.O. and the rather contradictory views resulting from clinical

observation, only a few aspects of this problem can be discussed.

Most venereologists agree, that obligate pathogenicity of P.P.L.O. is improbable.

It has been demonstrated that P.P.L.O. can be isolated from the urogenital tract, and also from the mouth of a large percentage of healthy people. The oral and genital strains definitely belong to different species, and sub-groups can be differentiated also among the genital strains. Cultural, morphological and serological properties of the strains are variable. Experimental investigations because of difficulty in using animals for this purpose, have not played an important part in elucidating the role of P.P.L.O. in the cause of Urethritis of Non-Gonococcal origin. The fact, however, that P.P.L.O. could be pathogenic must be considered until it has been proven beyond doubt, that they are saprophytic strains. This could mean, that under special circumstances P.P.L.O. could have some role in the production of some cases of N.G.U.

Ruiter[63] advances the following observations as an argument in favour of P.P.L.O. being pathogenic in cases of N.G.U.

1) The ocurrence of these organisms in pure culture (this having been observed in a number of cases in both males and females).
2) The disappearance of the organisms and the clinical response to treatment after administration of certain antibiotics, to which P.P.L.O. are susceptible.
3) The finding of P.P.L.O. in cases of N.G.U. resulting from sexual intercourse and the demonstration of similar organisms in the contacts of the patients.

The significance of these arguments is of course relative. The most interesting conclusion seems to be the pure cultivation of P.P.L.O., which has been observed in a number of cases of urogenital infections. In observing a few cases of previously untreated N.G.U. in males, I have been impressed by the dense growth of almost pure P.P.L.O. colonies, which appeared on the aerobically as well as anaerobically incubated media. It is conceivable, that the growth and the pathogenicity of P.P.L.O. in the urethral mucosa is dependent on the pH. of the surroundings as we know, that satisfactory growth of this organism on artificial media is largely influenced by the pH. of the media used.

To consider P.P.L.O. as pathogenic in man more than one contributing factor may have to be envisaged. Edward(117) observed that a P.P.L.O. strain isolated in cattle could only be grown on artificial media in the presence of vaginal mucus. It may be possible that similar factors also promote growth of P.P.L.O. on the genital mucosa in man. It may be recalled in this connection, that from my own investigations P.P.L.O. probably do not grow on the healthy mucosa as P.P.L.O. could not be grown in 19 control cases.

To this point, there has been drawn from the literature and my own work some theoretical support for the pathogenicity of the organisms of P.P. group.

In recent years there has been increasing evidence that the urethral P.P.L.O. are mostly mere saprophytes or commensals. P.P.L.O. are discovered now in abundance not only from patients with N.G.U., but also from males suffering from acute Gonococcal Urethritis, subclinical N.G.U., epididymitis without urethritis and controls with no genital abnormality.

The workers, who have discovered this, are numerous and increasing rapidly. Some of them (Freundt 1956) state, that P.P.L.O. are frequently part of the normal flora of the urethral orifice and the prepuce, and that their role in N.G.U. is quite negligible. Regardless of the clinical diagnosis, a definite correlation is now more often found between the ocurrence of P.P.L.O., and the number of ordinary bacteria. Some of the authors claim, that the incidence of P.P.L.O. is significantly higher in groups of individuals with smears rich in bacteria. Freundt (1956) gives the following data - "out of total of 87 males yielding relatively "abacterial" smears, P.P.L.O. were isolated from only 15 (17.2%), while 49 P.P.L.O. positive cases (64.5%) were found among 76 patients apparently harbouring large numbers of bacteria at the external urinary meatus and the fossa navicularis".

Freundt(1956)[68] in his recent work agrees with what other workers (Melen and Linnros 1952, Nicol and Edward 1953, Durel et al. 1954 and Shepard 1954,) namely, that no relationship could be demonstrated between the ocurrence of P.P.L.O. and the clinical type of urethritis or character of the discharge. The significance of a definitely lower incidence of P.P.L.O. in chronic N.G.U., than in acute cases found by Freundt is supported by Harkness (1950), who report "a much higher percentage of positive cultures" in the early acute phase of N.G.U. in Reiter's syndrome, than later in the disease.

It would thus appear, that while in the normal urethra the conditions are fairly favourable for the prevalence of P.P.L.O., the organisms are probably suppressed during inflammation, whether this be caused by gonococci or other agents, and the longer the urethritis lasts the greater is this suppression. The cause of this suppression of the P.P.L.O. remains obscure. It apparently

can not be ascribed to the migration of leucocytes, as no correlation was found between P.P.L.O. and the number of leucocytes present. The P.P.L.O., which usually behave as a saprophyte, possess a certain amount of pathogenicity. This is apparent both in males and females. Their pathogenic action is similar to that of the common bacteria of the mucous membrane. They seem to be pathogenic only under certain conditions. It is impossible to decide at present, whether they play a role in the origin and maintenance of Non-Specific Urethritis, but their pathogenicity in other sections of the genito-urinary tract e.g. cystitis and pyelitis suggests, that in some cases they may also be pathogenic in the urethra. These are reasons for retaining the P.P.L.O. as a probable cause of N.G.U.

While demonstration of P.P.L.O. in smears probably requires considerable experience, the culture method gives clear results, and at the same time provides an impression of the density of growth.

Personal results with P.P.L.O.

For a long time I was unsuccessful in obtaining positive cultures of P.P.L.O. The reasons for this were:-

1) Lack of practical experience.
2) Remoteness from laboratory facilities of both V.D. clinics in which I was working. The specimens were collected by swabs and subsequently inoculated in cultures, and transferred to the incubator in the bacteriological department. The time between the collection of the specimen and inoculation was sometimes several hours.
3) Changes in temperature to which the specimens were exposed.

4) Probable incorrect cultures e.g. their moisture, temperature, freshness etc., although, I was using different cultures recommended by other experienced workers. The placing of swabs in the medium, as described by Moffat et al. in 1948[13] for the transport of gonococci was also unsuccessful.

5) Improper reading of the culture.

All these errors and faults contributed to unsuccessful attempts to isolate P.P.L.O. It was extremely difficult to persuade the patients to report direct to the bacteriological department, where conditions for collecting the specimen and further investigation were excellent. This was especially so, when the patients were told that their diseases were not of venereal origin. As was mentioned previously, cases of pure Abacterial Urethritis in my experience were very rarely seen. The same opinion has been expressed by all of my colleagues, working in V.D. clinics in the Glasgow area. Sometimes I have waited two or three weeks for a suitable case of an Abacterial Urethritis.

Cases with Bacterial N.G.U. were often seen but rejected for P.P.L.O. investigations. In these cases other bacteria were present in the urethral discharge, and it was considered, that these had caused the urethritis, so cultures for P.P.L.O. were not taken despite the fact that P.P.L.O. might also be mixed with these organisms.

In some patients P.P.L.O. were found only in Giemsa stained preparations, but were not confirmed by cultures. They also have been rejected and not taken into account in my results.

After cultures of P.P.L.O. had started to grow my work in the V.D. clinics was reduced due to unforseen circumstances.

For the last year of my research I have had the opportunity to work only one afternoon and one night per week in V.D. clinic. Specimens from suitable patients could be taken only during the afternoon clinic and therefore, I was forced to turn to the gynaecological and maternity departments for further investigations for P.P.L.O. These, being situated in the large hospitals, gave me very satisfactory sources for further studies.

Unsuccessful cultures for P.P.L.O. have been performed in 53 cases of pure Abacterial Urethritis and in 19 controls. Nineteen of these cases, 11 with Waelsh type and 6 with Hecht type of urethritis and 2 from the control group showed positive P.P.L.O. in the Giemsa stained preparations but were not confirmed culturally.

The first positive P.P.L.O. culture was obtained from a single man, aged 38, who had no previous attacks of urethritis or venereal disease, and who had never been treated with antibiotics apart from a course of sulphonamide tablets several years ago for furunculosis and again one week before attending the clinic. His urethritis, which appeared on the twenty-eighth day after casual sexual intercourse was clinically typical of Waelsh urethritis, and showed microscopically only multple pus cells and epithelial cells. A specimen was collected by a dry sterile swab as at this time I was using swabs inserted into serum or into carrier media, and half an hour later was delivered to the laboratory and inoculated on culture medium.

The culture medium, which was fresh and moist, consisted of 5% rabit blood in agar in the presence of CO_2. After twenty four hours incubation at 37°C., small, just visible colonies appeared, which in another twenty-four hours increased a little more in size. An impression

preparation, according to Klieneberger, was made and multiple pure colonies of a sponge like appearance with minute bacilli form and coccoid bodies at the periphery were found. This culture was later on sub-cultured on moist, aerobic 5 - 10% horse blood, agar meat digest extract. It was also sub-cultured on horse serum, ox-serum, and the patient's own serum, and gave very abundant and pure culture. Sub-cultures have been performed twice weekly, and there is now a forty-fifth sub-culture on the aerobic 10% horse blood agar culture flooded with 200 units of penicillin.

The original cultures from this patient and also from several other positive cases of P.P.L.O. obtained from patients in the Gynaecological department were lost some time later, when the temperature in the incubator rose above 37°C. due to some electrical mishap.

From March to May 1957 another 12 cases of clinically and microscopically typical Abacterial Urethritis have been investigated, but cultures in all of them were negative for P.P.L.O. At this time the Gynaecological and Maternity departments started to send specimens from all suspicious patients for P.P.L.O. and other organisms investigation. Specimens and swabs from vaginal and cervical discharges were inoculated almost immediately onto exactly the same cultures, namely, 10% horse blood, agar meat digest extract, which were kept moist and aerobic and flooded with 200 units of penicillin. These cultures were incubated for at least forty-eight hours at 37°C. In each case impression sections were performed as follows:- a half square inch of a suspicious area of the culture was covered with a sterile coverslip, which was gently pressed on to the surface of the culture. The coverslip was then flooded with Bouin fixation fluid for ten minutes. The coverslip after this was lifted

carefully off the medium with forceps, without, sliding it on the surface, and washed in water for three minutes. It was then washed in acetone free alcohol for 1 - 2 minutes and stained with 5% Giemsa for five minutes. It was finally washed again in water for two to three minutes, dried by flame and sealed to the slide with D.P.X. (Distrene Dibutyl-phthalate Xylol), and examined under the low power of the microscope.

There were 14 positive cultures of P.P.L.O. in 42 females (33.3%) until the beginning of May 1957. They varied from 17 to 62 years of age, 40 were married and 2 were single. Six cases suffered from post puerperal pyrexia, 4 from vaginitis, 2 from menorrhagia, and one each from unexplained pyrexia and leucorrhoea. In 9 of the postive cultures only P.P.L.O. appeared on the culture plate. Five of these patients suffered from post puerperal pyrexia, 2 from unexplained vaginal discharge, 1 from menorrhagia and 1 from leucorrhoea.

In 5 positive cases cultures showed in addition to P.P.L.O. : a) Döderlein bacilli - 2 cases, b)Staphylococcus - 1 case, c) Coliform - 1 case, d) Staphylococcus and Influenza - 1 case.

Twenty eight patients from 42 gave negative cultures for P.P.L.O. In 19 (67.8%) of these cases the cultures were sterile while the remaining 9 cases (32.1%) showed on cultures:

a) B. coli -3
b) Staphylococcus aureus -1
c) Yeast -1
d) B. coli, enterococci-yeast -1
e) Haemophilus vaginalis -1
f) Enterococci and B.coli -1
g) Staphylococcus albus -1

These twenty eight females suffered from: chronic salpingo-cophoritis, menorrhagia, menopausal-menorrhagia, cystocoelle, rectocoelle, infertility, metropathia, leucorrhoea, monilial infection, trichomonas vaginitis. In only one case on direct examination was trichomonas vaginalis found.

It is striking, that 19 of these patients, who were negative for P.P.L.O. had sterile cultures; it is also interesting to note, that not only patients with post puerperal pyrexia and positive P.P.L.O., but all other patients with positive P.P.L.O. had had elevations of temperature. I have never observed an elevation of temperature in males with positive P.P.L.O. not in others with typical clinically Abacterial Urethritis with negative cultures for P.P.L.O.

Fixation tests[116] were made on a small group of (10) cases, in which P.P.L.O. were isolated. Antigens were prepared by centrifuging, in an angle centrifuge at 4000 r.p.m. for 2 hours 5 day cultures of P.P.L.O. growth in 10% (human) serum broth. The deposit was resuspended to 1/20th of its original volume in normal saline. In all cases complement fixing antibodies were present. The highest titer was 1/8, but according to J. Stokes[66] higher titers might have been obtained, if centrifuging had been carried out at 14,000 r.p.m.

Organisms of P.P. group seem to be organisms "per se" and connected neither with bacteria nor with any virus. Many excellent papers written on that subject (Klieneberger-Nobel, Edward 1954, and others) showed a clear difference between P.P.L.O. and bacteria in its "L-form". P.P.L.O., which are obtained from a large percentage of urogenital discharges, and from completely healthy people, seems to be saprophytes in the human body. Saprophytes,

which under certain conditions can become pathogenic, and produce serious inflammation and its complications. The complications are aggravated by frequent relapses of the acute inflammation even without further sexual relations.

The problems of P.P.L.O. poses many questions such as:

1) Why do we find P.P.L.O. in some cases of clinically and microscopically"Abacterial Urethritis", while in others they are absent?.

2) Why is P.P.L.O. in some urethral discharges found together with other organisms including: gonococci, spirochaetes, inclusion bodies and trichomonas vaginalis ?.

3) Why does P.P.L.O. sometimes disappear spontaneously from the urethral discharge, while it remains clinically unchanged ?.

No reasonable answer as yet has been found to these problems.

P.P.L.O. in male urethritis is contracted by sexual intercourse. All precautions, which are observed in the treatment of gonococcal infections, have to be observed also in this disease. We have to advise against intercourse, alcohol and from excessive use of motor-cycling and horse-riding. We cannot foretell in which patients the urethritis will disappear spontaneously and, therefore, all of them must be treated when P.P.L.O. and/or other organisms are found in the urethral discharge; the presence of pus cells only in the discharge is sufficient to restrict treatment. The partners of the patients, if known, should be treated as well as the patients themselves..

The treatment of choice is: oxytetracyclin (terramycin)

and tetracycline (aureomycin). A full description of the treatment is given in the chapter of "Abacterial Urethritis".

In the event of failure or relapse, the traditional treatment for chronic urethritis remains obligatory i.e., urethroscopy, urethral dilatation with prostato-vesicular massage, and Physiotherapy. The latter is important in order to prevent the patient becoming obsessional about his urethral discharge.

The social importance of Abacterial Urethritis is well known to specialists, but perhaps not sufficiently well known to the medical profession in general. For the patient the presence of so-called "Amicrobial Urethritis" is much more unpleasant, than an acute attack of gonorrhoea. The latter can be cleared up in a few days, whereas, the former, frequently badly diagnosed, persists for a much longer time, and can only be cured by treatment, which is sometimes difficult to endure. Complications are not too rare, and relapses are frequent. Many of these patients become obsessed with the complaint, and tend to develop into severe neurotic subjects.

Durel[82] aptly sums up the position as follows: "While it is agreed that Gonorrhoea is still a danger (venereal) for the individual, there is no reason for saying, that N.G.U.(Bacterial or Abacterial) does not represent at least as great a danger".

F. Prostatic Investigations.

Cytological investigations of the secretion of the prostatic gland for diagnostic purposes (Ferguson and Gibson),[97] is well recognised as a branch of histology requiring special experience. It is necessary to be able not only to differentiate between normal, degenerating, and pathological cells exfoliated from a specific source, but also to distinguish these from contaminants derived from adjacent excretory passages. In these respects examination of the prostatic smear demands particular experience, since the material obtained by the usual method of massage, or from the centrifuged urinary deposit, is often deficient in characteristic cells and may be heavily contaminated from the seminal vesicles. Nevertheless, if prostatic massage is conducted in a systematic manner and the ensuing secretion selectively examined, a reliable estimate of the condition of the gland can often be obtained. All these precautions in investigation of prostatic glands and prostatic secretions should be observed, especially in elderly patients (about 50 years of age and over) for possible finding and elimination of cancer of the prostatic gland or bladder, (Thomson 1873, Mulholland 1931, Papanicolau 1946).

The normal prostate is composed of two well defined zones of glandular tissue, an inner and an outer, surrounding the prostatic urethra. Each zone is characterised by a relative paucity of glands in the sagittal plane anteriorly, thus allowing a cleavage to develop under certain conditions. The two glandular zones are functionally quite distinct, particularly as regards their response to excess or lack of sex hormones. It would appear, that whatever aetiological factors are involved, the inner zone of stroma and glands is particularly prone

to benign hyperplasia, while carcinoma almost exclusively affects the outer. Accepting these facts it is easy to understand how the growth of "adenomata" from the inner zone may bring about a backward and downward displacement of the outer zone glands, thus forming the so called "posterior lobe". For cytological examination the apical region of the prostatic gland is most important, since cells expressed from this level will tend to be derived almost exclusively from the outer zone glands.

The most convenient way to obtain a diagnostic smear from prostatic massage is to have the patient standing with legs apart, facing the examination couch, and bent forward from the hips so that he can steady himself with one hand. If necessary he can keep the prepuce retracted with his other hand so that the operator can perform the massage and take the smear without additional assistante. The operator massages with his right index finger, and watches the previously cleansed external meatus for signs of prostatic fluid. To eliminate contamination from the mucous membrane of the urethra e.g. pus cells and other organisms, found in previous examination, the patient is told to urinate and his urethra is washed several times with tepid normal saline solution immediately before the prostatic investigation.

The method of expressing the prostatic secretion is very important, and is based on anatomical and physiological considerations. To diagnose carcinoma in elderly males secretions from the apex of the gland is most informative. On the other hand the secretion from the base of the gland is important in patient with Abacterial Urethritis especially in the younger age group.

Massage is begun as far forward as possible on the

side at the level of the first step near the apex of the gland. Pressure is applied as firmly as the patient can suffer, and the finger is slowly passed along the step towards the median groove. This movement is repeated several times at the same level on both sides of the gland. Similar massage is then performed at the level of each successive step, finishing at the base of the prostate superiorly. This allows the secretion to enter the urethra and thence to appear at the external meatus. This first secretion is derived from the apical region. The succeeding fluid will likewise consist of secretion from the middle and base of the gland with increasing vesicular contamination. Having completed the massage, the finger gently presses the urethra from above downwards, following as far as possible on to the bulbous urethra, through the rectal wall. The technique of obtaining prostatic smears has been described in detail, because of its very great importance, and should always be done by the investigator or a very experienced attendant.

Successive drops of secretion are now placed on the slides and a thin film of the secretion is produced. These are then placed in fixative solution or inserted on carrier media for culture.

There are certain contra-indications to prostatic massage. This includes a) acute urinary retention, b) bladder spasm, c) prostatic tenderness, especially, when combined with enlargement of the gland, and d) rectal spasm.

Before the days of sulphonamides and penicillin, gonorrhoea was nearly always followed by prostatitis

especially if it affected, and it usually did, the posterior urethra. Prostatic abscesses were not uncommon.

Since the introduction of penicillin the disease, if treated early, is usually confined to the anterior urethra, and the posterior urethra and the prostate escape infection in most instances. Nevertheless, chronic prostatitis is still diagnosed frequently, and it no doubt follows some form of genito-urinary infection. A recent article by three U.S.A. Army Medical Officers[98] suggests, that the usual symptoms of low back pain and heaviness in the perineum even if accompanied by a considerable number of pus cells in the prostatic secretion do not necessarily validate a diagnosis of chronic prostatitis.

The presence of 15 or more pus cells per high-power field in the prostatic secretion was considered by these investigators to indicate a diagnosis of prostatitis.

In my series of 103 cases of Abacterial Non-Gonococcal Urethritis - 27 (26.2%) had prostatitis or showed evidence of prostatic infection. Of these 27 cases 9 came from the Hecht sub-group, and 18 from the Waelsh sub-group of urethritis.

As described previously in the Hecht sub-group, 1 patient developed acute prostatitis. "Asymptomatic" prostatitis was found in one of 2 patients, who had suffered previously from gonorrhoea. Another 3 cases of "asymptomatic" prostatitis were found in patients previously treated with penicillin for diseases other than gohorrhoea and finally in 3 patients with epididymitis.

In the sub-group of Waelsh urethritis 18 cases were found with prostatitis and positive prostatic secretions.

Three patients had been previously treated with penicillin for gonorrhoea, and 4 cases had previous penicillin therapy for diseases other than gonorrhoea. Two cases were complicated by epididymitis, and 9 cases had "asymptomatic" prostatitis. It was impossible to obtain from these 9 patients exact information concerning their treatment. They had received some drugs (probably sulphonamides) and penicillin, for an infection other than gonorrhoea.

It is striking how high a percentage of prostatitis was found in this group. In 13 cases (12.6%) it was a true "asymptomatic" prostatitis. In these patients prostatic secretions from an apparently normal gland showed an abnormal number of pus cells. In the remaining 14 cases the prostatic glands were on palpation, soft or hard, and boggy or painful.

Prostatitis is synomous with inflammation of the prostate, and where there is inflammation there will also be pus cells. If, therefore, a specimen of prostatic secretion contains an abnormal number of pus cells, it may be assumed that prostatitis is present. Opinions differ on what is an abnormal number of cells, but in my opinion more than 5 cells in the high power field constitutes an abnormal count. Prostatitis comprises both symptomatic and asymptomatic forms of the disease. Symptoms are often a poor guide. The patient who reports with low back pain, heaviness in the perineum, disturbances of micturition, or impotency, may be one, who has been exposed to or suffered from urethritis or, who is mentally upset. Digital examination of the prostate may or may not confirm the diagnosis. If the organ is soft and boggy,

it is obviously abnormal, but in mild chronic cases little change can be detected and reliance must be placed on history, symptoms and the results of pathological examinations.

Many cases will clear up with treatment such as: abstinance from alcohol, temporary cessation of sexual intercourse and no cycling. In some cases Mist.Potassium Citrate (B.P) by mouth settles the inflammation. Some cases will clear up after gentle massage of the organ, repeated every 5 - 7 days for a few weeks, followed by irrigation with 1/8000 oxycyanate of mercury. When the patient is nervous and over anxious, reassurance, a placebo, or perhaps a sedative may hasten recovery.

This high percentage of adult males with silent chronic prostatic inflammation may cause one to consider the possibility of the previously inflamed prostate being an important factor in the genesis of N.G.U. Certainly, the individual with known chronic prostatitis, who has an exacerbation associated with a muco-purulent discharge, is indistinguishable from the individual, who is seen in the V.D. clinic with what is thought to be primary N.G.U. Urologists have recognised for many years patients with demonstrable inflammation, whose only sign or symptom was recurrent urethral discharge, frequently unrelated to recent sexual exposure, but more frequently related to alcoholic excesses, long bicycle rides, fatigue or an illness such as an upper respiratory tract infection.(28)

It is possible that the urethral discharge seen in N.G.U., represents the initial conspicuous sign of a process, which has been harboured for some time by the patient and now revealed only after certain ecological relationships have been altered resulting in greater

activity and extension of the silent infection to adjacent tissues and structures.

G. Urine Investigation.

The chemical examination of the urine was limited to litmus paper. Except for a few cases with transitory alkaline reaction after meals, the urine was acid in reaction. In two cases a chronic deposit of phosphates was noticed in slightly alkaline urine. This was eradicated completely after one gram of ammonium chloride daily for 1 - 2 weeks. In both cases the disappearance of phosphates and return to acidity of the urine had no influence on the urethritis of the patients.

H. Urethroscopy.

An aerourethroscopic (Harrison) examination was performed in 16 of the 82 cases before treatment was started, and in all 82 patients after treatment, as part of the test of cure. Seven of the 16 cases were of the Hecht variety of urethritis, and the remaining 9 were of the Waelsh type.

Six of the 7 cases of Hecht Urethritis showed on aerourethroscopy a general redness and inflammation of the mucous membrane of the anterior urethra. The seventh case showed the typical superficial excrescences more commonly seen in Waelsh urethritis.

Seven of the 9 cases of Waelsh Urethritis revealed on aerourethroscopy white, greyish excrescences, lying chiefly on the roof and lateral walls of the urethra; these appeared to lie superficially on the mucous membrane, and there was no obvious involvement of the sub-epithelial

tissue as seen in gonorrhoea. There was also some involvement of the glands of Littré, and the intervening mucous membrane was as a rule red and inflamed. In the remaining 2 cases there was a general redness and inflammation of the entire mucous membrane. The typical cobble-stone appearance (likened to trachomatous nodules) was found on further urethroscopy in 4 of the first 7 cases, just before the treatment was started 7 - 9 days later.

Harkness in 1950 stated "If all venereologists were skilled in using the anterior urethroscope, urethral strictures would rarely follow gonorrhoea or gonococcal urethritis".

It was decided in late 1956 at the meeting of Venereologists of the Glasgow area to postpone urethroscopy as part of the test of cure in all patients with primary, uncomplicated, acute gonococcal urethritis, who had been treated successfully with a single dose of 300,000 i.u. of procaine penicillin. In several hundreds of cases of acute gonorrhoea aerourethroscopy (Harrison's type) performed as a part of the test of cure, had showed no abnormality in almost 100% of cases. The mucous membrane always looked healthy, moist, smooth and glistening. In very rare cases and especially in those who previously had had gonococcal urethritis, the mucous membrane showed some redness; also, very occasionally, so called "urethroscopic strictures" were found. In other cases (complicated gonorrhoea, non-gonococcal infections, both bacterial and abacterial) urethroscopic examination was recommended.

My own opinion differs from the above recommendation. I would say that not only urethroscopy, but also bougie examination and investigation of the prostatic gland should

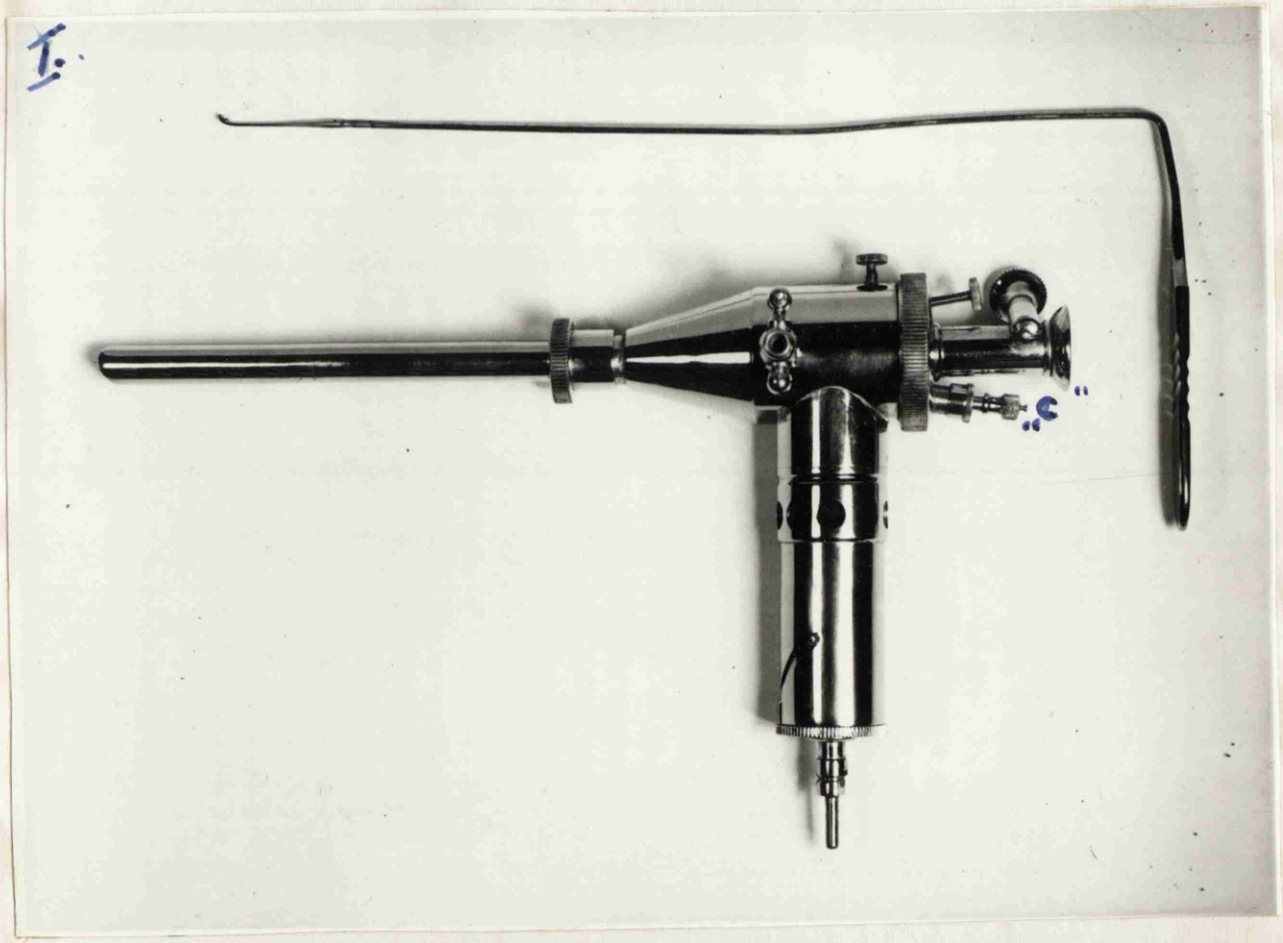
be done in all these cases as a part of the test of cure. Information obtained from urethroscopic examination is much more accurate, than that obtained from only bougie examination. A stricture, however, situated in the distal part of the urethra (pars membranacea), can be detected by the curved sound. By using the curved sound I found in several cases strictures situated only in that part of the urethra. Therefore, both these investigations must be performed.

The doctor must be more satisfied, if he can discharge a patient after full investigation has revealed no hidden focus of infection, which in the future might produce some complications.

In a number of cases of Abacterial and Bacterial Non-Gonococcal Urethritis, a modified type of Swift-Joly urethroscope was used. I intended to take material blindly from the urethra by a sterile swab and also use the urethroscope to collect material from any patchy or confluent inflamed area, which might be seen in the urethra. It was hoped that a difference might be found in the material taken by these two methods, and that the material obtained by the urethroscope could be used for inoculation on to a culture medium and/or examined under the microscope.

In my modification of the Swift-Joly urethroscope, the needle, which in the pre-sulphonamide and antibiotic era was so often used for electrolysis in post gonococcal Littre'itis and chronic gonorrhoea, was elongated a little over one inch, and ended with a small cup. The edge of the cup was fairly sharp and large enough to scrape and collect a sufficient quantity of tissue for investigation. By lengthening the needle manoeuvre ability was greatly improved.

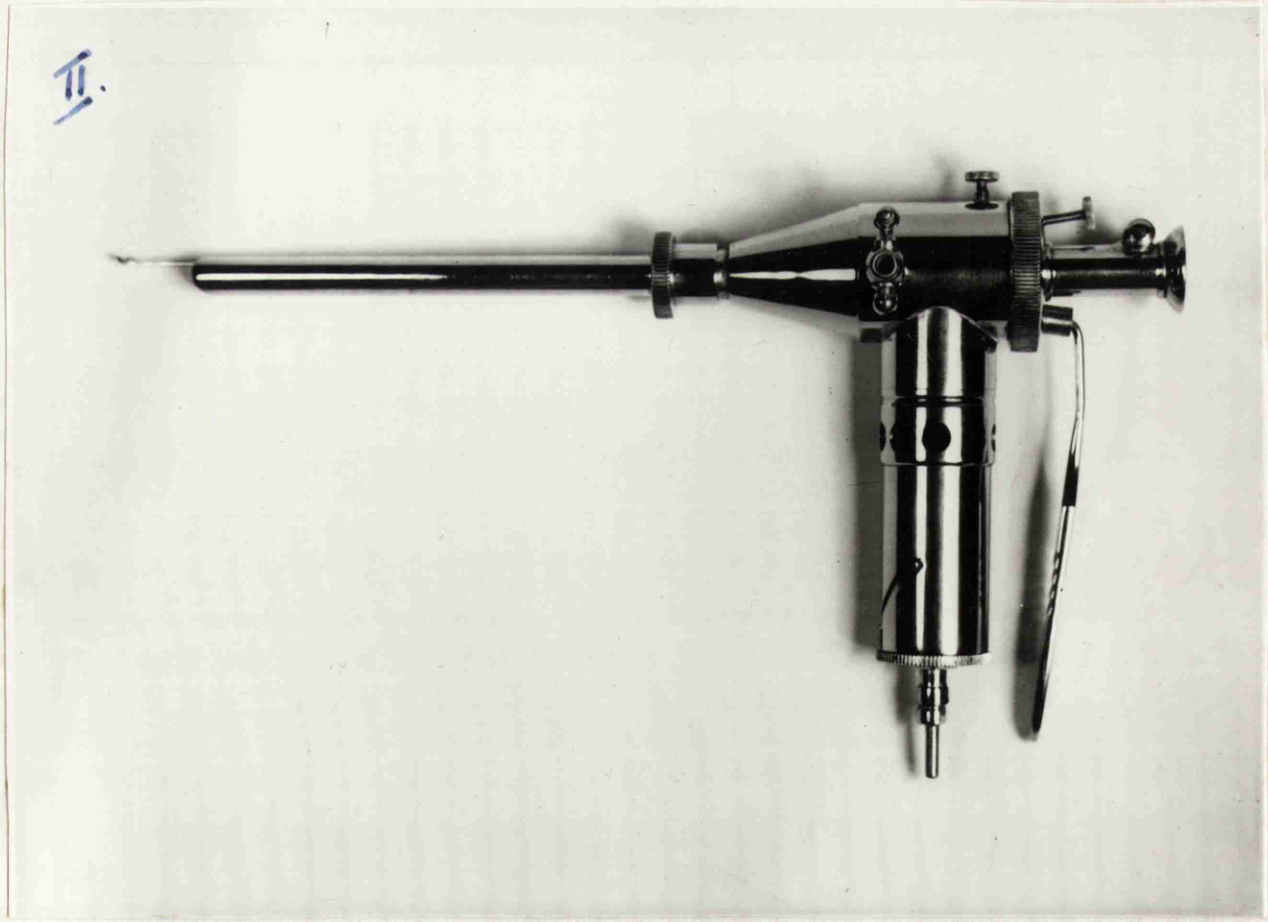
The photograph below shows the Swift-Joly urethroscope, and separately the elongated and modified needle.



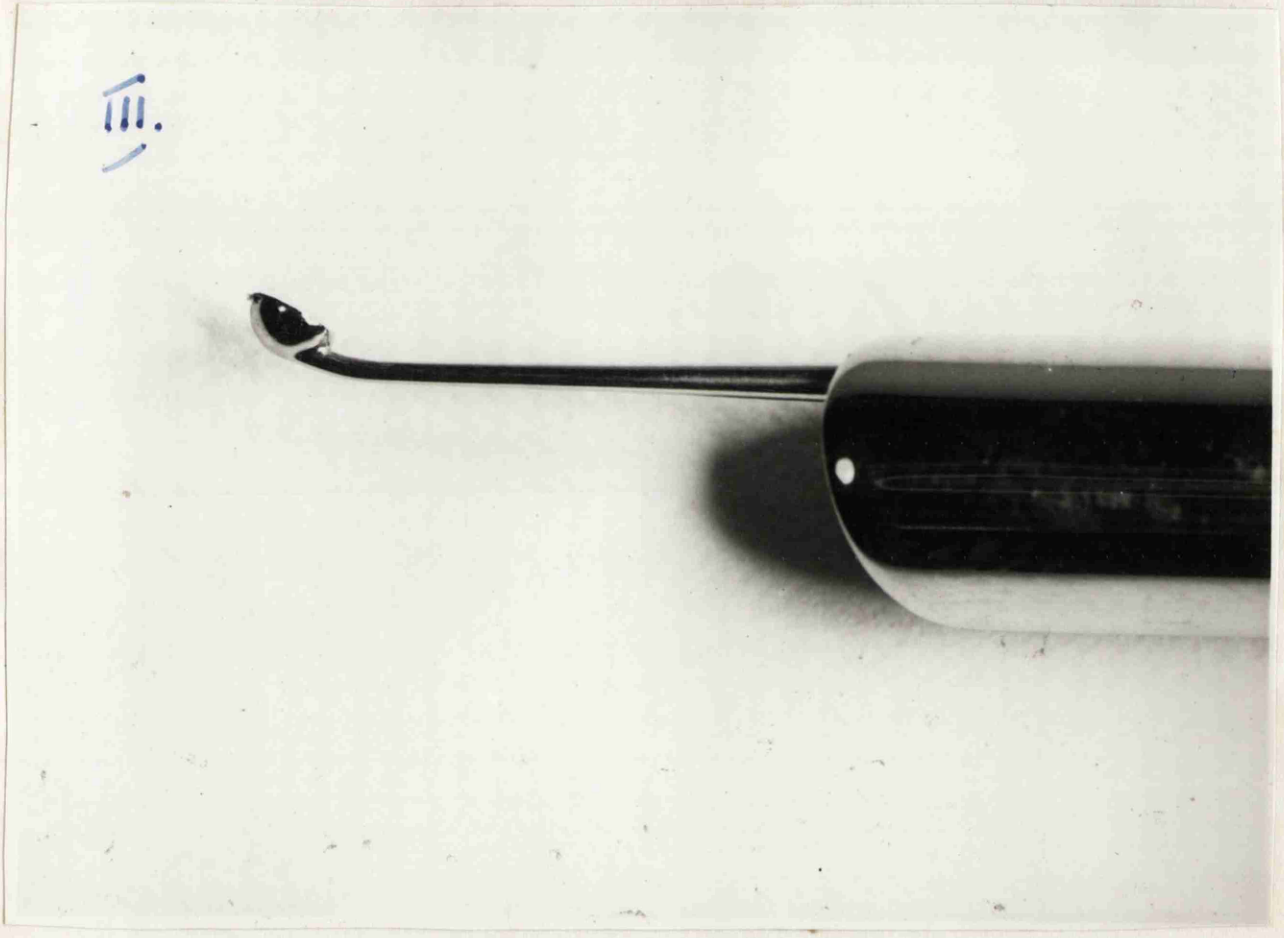
There are three different sizes of urethroscope tube, but even the smallest tube gives a good view and allows for ease of handling.

The patient only partially empties his bladder, his external meatus is cleansed with 1/4000 oxycyanate of mercury or methylated spirit. The lubricating tube with obturator in position is passed to the bulbous urethra. The obturator is withdrawn and a sterile swab is passed to mop up the excess of lubricant. If the swab is blood-stained, the tube is withdrawn and examination

postponed. When an obstruction, even the slightest one, is experienced in passing the instrument, the obturator must be withdrawn immediately. If no obstructions are met the urethroscope with the light already focussed is then attached to the tube. Now the small cup of the nipple "C" (marked on the No.1 photograph) is withdrawn, and the needle is inserted through the hole, as shown in photograph No.11. The needle is brought to the end just to demonstrate its length.



Photograph No.111.is enlarged to show the end of the needle.



The operator hold the urethroscope in his left hand and the needle in the right hand with the end of the needle still inside the tube. He manoeuvres the tube gently, until he finds a suspicious lesion or infiltration on the mucous membrane. He then moves the needle forward a little outside the tube, and with one gentle movement of the needle scrapes some material into the cup. After this has been done, he immediately takes the needle away from the wall of the urethra and quickly up the tube. It is important that, the scraping should be done as quickly as possible.

The operator now examines the area previously scraped. Usually there is a small slightly bleeding mark. He then withdraws the urethroscope and inspects carefully the roor and lateral walls of the urethra. After withdrawing the urethroscope, the operator watches the external meatus for any discharge and gently massages the urethra to observe, whether any discharge especially blood appears. In my experience bleeding from the urethra was very scanty and stopped usually in a few minutes. The patient is now told to pass urine retained in the bladder. In my cases it was not necessary to wash out the urethra with normal saline after this procedure.

All excoriations made by scraping healed well in about two days, and did not produce any complications e.g. strictures.

The lubricant used for urethroscopic examination was 2% Xylocaine gel. This also has the advantage of partially anaesthetising the mucous membrane. The patients tolerated the examination well, and the material was sufficient for further investigations and consisted not only of epithelial elements, but also had sub-epithelial tissue in it.

I do not recommend this kind of combined urethroscopy and scraping as a rule. I have been using it "experimenti causa" only, but in some rare cases such as: papilloma or carcinoma of the urethra, material gained very cautiously by this method from the suspicious lesions, might be of great value.

It is well known, that it is very dahgerous to instrument the inflamed urethra. Therefore, patients for urethroscopy and scraping have been carefully selected.

Clinical and microscopical examinations were carefully and fully done previously to urethroscopy and the cases classified as Abacterial or Bacterial Urethritis, and immediately after the scraping - treatment was started. Fortunately, there was no aggravation and complication in the patients condition after scraping was performed.

The modified Swift-Joly urethroscope was used in 7 cases of abacterial urethritis, 5 cases of bacterial urethritis and 4 cases (controls).

This is a small number of cases, but surficient in my opinion - from which to make certain deductions.

In the 7 cases of Abacterial Urethritis 5 cases had inclusion bodies in Giemsa stained slides, 2 of which were confirmed by Fuelgen; a specimen from the sixth case was inoculated on the special medium, but with negative results; in the seventh case urethroscopy had had to be postponed, because of bleeding. Obtaining 5 positive specimens in 6 investigated - would appear to be a very satisfactory result, when compared with the method in which a loop or swab is used. The specimen for inoculation on the medium was collected from the tiny cup by a sterile swab and inserted in the first place in chocolate carrier medium. In 3 of the 5 cases with Bacterial Urethritis, Gram stained slides showed multiple mixed micro-organisms. Second slides from the same 3 patients stained with Giemsa, confirmed the presence of multiple micro-organisms, but inclusion bodies were not found. Specimens from the remaining 2 cases were collected by swabs and inserted into Stuart carrier media and later inoculated on 10% chocolate agar media.

Both cultures revealed mixed growths of staphylococcus albus and diphtheroides.

In one of the 4 control cases - bleeding took place on examination and, therefore, this case was eliminated from further investigations. In 2 cases slides stained with Gram and Giemsa showed no micro-organisms or inclusion bodies, but only scattered epithelial cells and a few erythrocytes. The last case from the control group gave a culture of scanty staphylococcus albus, which the bacteriologist classified as a "saprophyte".

The only difficulty of obtaining material by the above method is, that the amount of the specimen contained in the cup is sufficient for only one investigation e.g. for one or two slides or culture, but not for both: slides and culture - at the same time.

J. Treatment.(99,102-105,108)

In the treatment of my series of "Abacterial Urethritis" the broad spectrum antibiotics, Terramycin, Aureomycin, Chloramphenicol and Rovamycin were given by mouth except for 7 cases, in whom water soluble Aureomycin was instilled locally into the urethra.

The choice of drug and the time of starting therapy was considered for each individual case. In those cases who had complications such as: acute prostatitis - Terramycin and Aureomycin was given as soon as possible. In cases with no complicating factors greater liberty and experimentation with treatment could be taken. All cases treated with antibiotics also received Vitamin B complex, to lessen gastro-intestinal irritation.

The results of therapy are shown in table below.

Antibiotic therapy in Abacterial Urethritis.

Antibiotics	Total Cases	Acute	Sub-acute	Successes. Acute	Sub-acute	% total	Failures. Acute	Sub-acute	% Total
Terramycin	22	5	17	3	16	86.4	2	1	13.6
Aureomycin	39	15	24	11	20	79.4	4	4	20.6
Chloram-phenicol	25	11	14	6	9	60.0	5	5	40.0
Total	86	31	55	20	45	75.6	11	10	24.4

In this group of 86 cases I have included all cases from sub-groups of the Hecht and Waelsh Urethritis, who developed during investigation some complication such as epididymitis. Also included are patients, who had received previous penicillin or antibiotic therapy, and also all patients, who were urethroscoped by the Swift-Joly scraping method.

The dosage of antibiotics.

1) Terramycin was given in 250mgm tablets, four daily for 5 days, together with Vitamin B - 3 mgm t.i.d

2) Aureomycin Capsules 250 mgm four daily for 6 days, together with Vitamin B - 3 mgm t.i.d.

3) Chloramphenicol Capsules 250 mgm, 4 daily for 6 days.

The table shows, that 21 of the 86 cases have been classified as failures to treatment. Eight of these cases defaulted soon after treatment was started. Four cases completed treatment, but stopped attending before the test of cure. The remaining 9 cases had recurrences of the urethritis after treatment. Of these 9 patients one who had a sub-acute urethritis relapsed three weeks after treatment. On this occasion the inclusion bodies which had been present in the first attack were absent, and the patient responded well to a second course of antibiotics. In another 2 of the 9 cases with acute Hecht type of urethritis, recurrences of the discharge appeared 14 to 17 days after treatment with aureomycin. Both cases admitted to drinking and sexual intercourse. Inclusion bodies although present during the first attack, were not found in the relapse phase, and both cases responded well to further aureomycin therapy. The remaining 6 cases, 4 from the Hecht sub-group and 2 from the Waelsh sub-group, relapsed 8 to 20 days after their treatment with chloramphenicol. Three of the 6 cases confessed to further sexual intercourse. Only 2 cases cleared with a second course of chloramphenicol. The other 4 cases required a course of aureomycin and this cleared the urethritis in all of them.

In the small group of 5 cases with urethritis complicated by epididymitis, 4 responded very well to treatment. Acute symptoms disappeared before the end of treatment, but for many months the affected epididymitis remained hard and tender. This is unlike post-gonococcal epididymitis, in which the organ settles very quickly after penicillin therapy.

Seven patients with Abacterial Urethritis were treated with an aureomycin solution instilled into the

urethra. Five cases were of the Waelsh sub-group, and 2, the Hecht sub-group. In only 2 cases of the former group were inclusion bodies found by Giemsa stain, but not confirmed by Fuelgen. All seven cases showed microscopically a typical picture with multiple pus cells and scattered epithelial cells. There were no other micro-organisms in repeated slides. Four patients were single, 3 married. Their ages varied between 34 - 47 and 2 of them previously had had gonorrhoea.

I started my experiments with an 0.1% aqueous solution of aureomycin. Ten cubic centimetres was instilled into the urethra with a sterile syringe, and the solution retained for 20 minutes. Two patients were under this treatment for three successive days. No change was noted, and before each instillation - smears revealed many pus cells and some epithelial cells. The next day, the percentage of the solution was increased to 0.3% and instilled for two successive days. Each day microscopical examination showed a marked diminution in pus cells and an increasing number of epithelial cells. The patients looked clinically different; the rather profuse urethral discharges became very scanty, and the patient felt much more comfortable. They did not feel any irritation nor burning sensation inside the urethra. After 2 days of 0.3% solution the strength was increased to 0.5%. This strength of solution stopped the urethral discharge after three successive instillations, and a specimen obtained by scraping showed only epithelial cells and no pus cells. The appearances were very like an exfoliative urethritis. The treatment was stopped for one week. In one patient a mild discharge appeared on the fifth day. Microscopically a few pus

cells and multiple epithelial cells were found in this. Instillations of 0.4% solution was administered for four successive days, and the urethral discharge disappeared completely. The second case became symptom free and remained so for the next six weeks, while under observation.

In the next 5 cases an 0.5% solution was instilled daily or every second day and the number of treatments varied from 1 - 7. Usually on the fifth or sixth instillation the patients became symptom free, and remained so for at least two months, when the test of cure was performed. In 2 of these cases urethroscope examination was not performed, because, of an intrameatal hypospadias. In the other 5 patients urethroscopy revealed no abnormalities.

This group of patients were especially selected. All of them were trustworthy, they obeyed all instructions and attended the clinics very regularly.

This preliminary work in my opinion indicates, that an 0.4% aureomycin solution, when instilled into the urethra of a patient suffering from urethritis gives a very satisfactory results. It could be a useful alternative form of treatment of Abacterial Urethritis in patients, who were intolerant to oral antibiotic treatment.

Another 4 patients, 3 with Waelsh Urethritis and 1 with Hecht Urethritis, were treated with Rovamycin (Spiramicin). Their urethral discharges showed on microscopy only pus cells and epithelial cells. In only one of these cases were inclusion bodies found in Giemsa and Fuelgen stained slides. Rovamycin tablets, 250mgm each were given four times daily for four days in 2 cases, and for 5 days in another 2 patients. The two patients who

should have taken tablets for 4 days, stopped the treatment on the third day, because, of severe diarrhoea. The remaining 2 cases also got looseness of the bowels before completion of the treatment. It is interesting, that in all these cases the urethral discharge disappeared completely, but reappeared in all cases a few days later. Microscopically, again multiple pus cells and scanty epithelial cells were found, but no inclusion bodies. Three of these cases responded very well to a course of aureomycin capsules and one to terramycin capsules. Benerva tablets were not given together with Rovamycin tablets, and so, the full result of this experiment and usefulness of Rovamycin has not been established.

The treatment of the three cases in which Trichomonas vaginalis was found is described on pages 69 - 73. Two cases which first presented as cases of abacterial urethritis and later became bacterial and finally developed into abacterial urethritis, are fully described on pages 86 -87.

Alcohol, sexual excitement and strenuous work or exercise were forbidden during investigation of the patient and for at least two weeks after treatment. Defaulters in the above regime and those who did not complete the prescribed observation period were eliminated from the series. Severe side reactions, such as acute diarrhoea were observed in patients treated with Rovamycin. Milder reactions such as: looseness of the bowels, and less frequently nausea, were noted only occasionally with terramycin and aureomycin, but more often with chloramphenicol. No blood-born complications or Herxheimer-like reactions developed during treatment.

Criteria of cure.

Before a patient was declared cured the following criteria were demanded:

a) No urethral discharge and a clear threadless urine. Under treatment with terramycin and aureomycin, the urethral discharge stopped approximately on the fourth or fifth day. In the patients treated with chloramphenicol a more delayed result was observed; in most of them the urethral discharge ceased on the completion of their treatment or in some cases a few days later. In a few cases a clear urethral secretion remained for several days. The urine was clear or contained only a few light mucous threads, which on microscopy revealed only an occasional leucocyte. These cases were regarded as cured, if the threads disappeared without further treatment.

b) Observation period: most of the cases were under regular observation for at least a month after antibiotic therapy.

c) Examination of the vesiculo-prostatic secretion and urethroscopy was carried out in all cases, except, for a few with intrameatal hypospadias. This was done in the sixth week after the completion of the treatment in uncomplicated cases, and in cases with complications such as: epididymitis or acute prostatitis-two months after the completion of the treatment.

d) A blood test (Laughlan)was performed at the beginning and end of treatment. In some cases

especially in those, who previously had contracted syphilis, Wasserman and Kahn tests were performed and in all cases who admitted gonorrhoea in the past, a Gonococcal Complement Fixation Test was also performed. In only one case did the G.C.F.T. become positive. This patient had had gonorrhoea eight years previously, had been treated with penicillin. He now suffered from (Waelsh type) sub-acute N.G.U. My effort to find a source of his positive G.C.F.T. was unsuccessful. A single course of aureomycin tablets cured his urethritis, but his blood for G.C.F.T. still remained positive.

Some venereologists in the Glasgow area do not think it necessary to treat patients with Abacterial Urethritis. They regard it as sufficient to tell the patient to forget his troubles, not to squeeze the urethra and to avoid alcohol and spices. I do not agree with them. In only a very few patients with Abacterial Urethritis does a psychological factor play the major role in its production. In these few patients correct psychological treatment by specialists is necessary.

I agree, however, that diet may play some role in the production of urethritis.

In my series of eighty two cases, I observed a very interesting phenomena. Three patients were told at the beginning of their investigation to avoid alcohol and spices and to abstain from sexual intercourse. They soon noticed a marked improvement and this was also confirmed by my own observations. In one case, the urethral discharge disappeared entirely in seven days, while the other two

ceased after one or two weeks. In all three cases the urethral discharge reappeared in the next 8 - 10 days. Only one patient confessed to drinking alcohol. The other two did not break the rules. The urethral discharge in two patients was very profuse, but scanty in the third case. Microscopical examination revealed in all three cases only pus cells and epithelial cells. Two of these patients had had several similar attacks of urethritis previously. One of these patients started to complain of some pain in the left testicle of two days duration. Clinical investigations did not reveal any swelling, but the left epididymis was slightly tender to touch. One day later a slight swelling of the epididymis was noticed, the tenderness had increased and patient was put immediately on treatment (Terramycin tablets 250 mgm four daily for four days). The urethral discharge settled down almost the next day, and on the third day the swelling and tenderness had disappeared completely. This patient was not investigated previously either per rectum or by urethroscope and he was not a neurotic type. He had not past history of any venereal diseases, but had had similar attacks of urethritis, the last attack being about three years before. He was married and had two children. His prostatic gland, when investigated two weeks later revealed no abnormalities and urethroscopic examination was negative. Smears from the urethral discharge stained with Giemsa and Fuelgen for inclusion bodies were negative, as was culture for P.P.L.O. I could not risk any further investigations, when the tenderness and swelling of the epididymis appeared. This patient obeyed all the orders given, and yet developed an early epididymitis without any obvious cause. This fortunately settled down well with the immediate treatment. It is also interesting that the onset of the

epididymitis started rather slowly and progressed slowly in comparison with epididymitis due to gonococci, in which the onset is usually very acute in all aspects.

In two other cases, treatment was established at the first visit, as in both of these cases the prostatic gland was slightly enlarged and tender and microscopical smears revealed multiple pus cells, some in clumps; cultures in both cases were negative.

One of these patients, a young twenty-six year old, married man, had been sexually very active; taking my advice seriously in certain respects, he withheld completely from sexual intercourse, but he had been drinking nearly every night. This excessive alcohol could have awakened his old even asymptomatic prostatitis, which he had contracted during previous attacks. It is the only explanation for his urethritis due to prostatitis, especially, when no organisms, inclusion bodies, or P.P.L.O. were found.

The last case, a married man, aged 38 with three children, had had gonorrhoea treated with penicillin in 1946, seven years before his marriage. His blood on examination was negative. He had been symptom free since then, and his sexual life was always very active. After he came under my care he did not drink and abstained from sexual intercourse for over three weeks and then suddenly developed a fresh out-break of urethritis, originating from his prostatitis. On test of cure no abnormalities were found and the patient was discharged. I lost contact with him. For a long time I could find no explanation for this patient's sudden attack of urethritis. A recent article of Dr. Harrison[112] offered me a clue, and I believe that it is the right one. This patient previously

had contracted together with gonorrhoea some infection of the prostatic gland. This was a symptomless prostatitis. His regular sexual intercourse during marriage had kept the prostate draining. Suspension of sexual intercourse for several weeks had stopped the drainage and the collection of pus, which had formed behind the blocked opening, had burst and discharged into the urethra.

The detailed description of these three cases indicates that the large majority of the cases with mainly Abacterial Urethritis (especially those who have had several attacks of urethritis) - require proper treatment. Recurrences and complications such as prostatitis and epididymitis occur quite often in these patients.

Instructions from the doctor concerning diet or abuse of the urethra in the absence of proper investigation and treatment, are of little value.

VII. SUMMARY.

In 1919 Willis[19] stated, that from statistics of the first world war 95.6% of cases of urethritis were caused by Gonorrhoea, while only 4.4% were of catarrhal origin. During the second world war the statistics showed that 35.6% of cases of urethritis were caused by Gonococci, while 64.4% were non-specific in origin. Taking into consideration the possibility of an erroneous diagnosis of Gonorrhoea in many cases in 1919 the change in proportion of these diseases is very striking.

Authors from other countries give very similar data from the second world war; sometimes the percentage of gonorrhoea is a little above that of Non-Gonococcal Urethritis (N.G.U.), but all agree that the percentage of N.G.U. has increased greatly in the last 10 - 15 years. As many workers have demonstrated it is remarkable, that this increase of N.G.U. is so closely connected with the advent of sulphonamides and antibiotics.

The incubation period of gonorrhoea itself has lengthened considerably, and is now on an average about eight days. Today, there is also an obvious increase in gonorrhoea in which the gonococci are mixed with other bacteria. Perhaps before the sulphonamide and antibiotic era it was the same, but our attention was absorbed with the gonococcal infection, as then its treatment was much more difficult.

The increase of N.G.U. appeared during the second world war with the advent of sulphonamides and antibiotics, when people (soldiers and civilians) had been treated for many different diseases with those drugs.

Some authors state, that sulphonamides and antibiotics, especially penicillin, are still used by non-medical ships officers. These drugs are often given in inadequate doses to any suspicious case of urethral discharge without any possible diagnostic tests being performed.

The use of sulphonamides and antibiotics in low doses for a variety of infections not only venereal, may bring relief of symptoms without cure, and this is a dangerous procedure from the venereologists point of view.

An analogous conception is found by other workers in the treatment of women e.g., some women may unknowingly harbour gonococci. During this, they may develop an acute tonsilitis, for which they receive penicillin lozenges. This is quite sufficient to cure tonsilitis, but not enough to kill gonococci. The latter become attenuated, but the drug given in such a small dose does not prevent them from being still pathogenic.

These workers have come to the conclusion, that gonococci can exist in some new ultramicroscopic form. They suggest, that the gonococci have been forced to change their normal form, because, of the large number of people treated with these drugs. They attributed all forms of N.G.U. to this altered type of gonococci or in other words state, that these cases are actually gonorrhoea, but in an altered and temporary phase. This theory may have been possible in the sulphonamide era, but in my opinion since the advent of penicillin it is no longer tenable.

Other workers theoretically discuss those cases in which numerous other organisms and pus cells are present in the urethral discharges. Undoubtedly, these types of urethritis are much more numerous today, than before sulpha-drugs and antibiotics. The other organisms may appear

singly or in groups as mixed organisms. The suspicion again arises, that possibly the sulpha-drugs or antibiotics in the infected female have caused the gonococci to disappear, but have rendered infectious to the male other normally harmless inhabitants of the genito-urinary passages. It should be possible to grow these organisms on culture, but even if this were done, it would not help us to find out why they have caused acute urethritis when planted in new soil?.

Glasgow is a big city and a port. It is astonishing that Bacterial N.G.U. is much commoner than Abacterial Urethritis. This is completely different from the results of many other workers, who find Abacterial Urethritis is commoner than Bacterial N.G.U. It would seem, that my results, which show a clear majority of Bacterial N.G.U. could even be increased, if by taking precautions in cleansing the external meatus of the urethra and in collecting the specimen, all pseudo or real saprophytes from the group of Abacterial Urethritis were excluded. A possible explanation of this is, that many patients have been treated by their panel doctors, thus making the official statistics inacurate. The opinion of other venereologists in Glasgow V.D. clinics are consistent with my figures.

In my search for P.P.L.O. (mycoplasma species), and inclusion bodies, I have examined mainly those abacterial types of urethritis. I have come to the conclusion that typical "Abacterial Urethritis" is a rare disease. It is not a seasonal disease as is gonorrhoea, which increases usually after holidays at New Year and at Easter. Occasionally, I had to wait several weeks before finding a typical case. In addition some of these patients, when informed, that they were suffering not from gonorrhoea, but " some kind of urethritis" defaulted from further attendance/

unless the discharge troubled them or the patient was intelligent enough to consent to have a "non-venereal urethritis" treated.

Whatever the organisms, I did not pay too much attention to bacterial urethritis, because: complications in the course of the disease are as a rule very rare; treatment is not difficult, and sooner or later they clear completely especially, when cultures and sensitivity tests have been performed, and recurrences are rare in comparison with abacterial urethritis.

Treatment of certain types of N.G.U. especially the abacterial type may involve some psychotherapy. Fortunately these patients are few, and most of them are easily persuaded to have treatment for their "imaginary" diseases. In only a few of them is a close collaberation between venereologist and psychiatrist necessary.

There is a strikingly large percentage of complications in Abacterial Urethritis in comparison with Bacterial Urethritis and Gonorrhoea itself. These complications are mainly: epididymitis and prostatitis. Epididymitis in "Abacterial Urethritis" was found in 5 out of 103 cases (4.8%). During the same period epididymitis was observed in only 4 cases in over 200 cases of gonorrhoea. I have found no cases of bilateral epididymitis. Prostatitis usually appears in abacterial urethritis as "asymptomatic" prostatitis. The patients as a rule do not complain of any pain in the anal region or of disturbances of micturition. Investigation "per rectum" in all these cases (especially in Abacterial Urethritis) is essential, and very often reveals abnormalities in the prostatic structure and prostatic secretion. Additionally taking into consideration recurrences,

which occur relatively often especially in "Abacterial Urethritis". I have come to the conclusion, that all kinds of urethritis have to be seriously investigated, and the big majority of them very thoroughly treated.

Our knowledge in some aspects is still very limited. This is especially so in regard to inclsuion bodies, where our present methods of study are very inacurate. In view of the fact, that our knowledge concerning the precise nutritional requirements of the P.P.L.O. group is not clear, it is safe to say, that a truly, appropriate, standardizable artificial culture medium has not thus been developed. Indeed, failure to isolate P.P.L.O. may reflect on inappropriate culture technique rather, than absence of the organisms in cases of N.G.U. Further, artificial culture media suitable for the isolation of "saprophytic" P.P.L.O. types from the mucous membranes may fail completely to grow those P.P.L.O. strains or species, whose nutritional requirements are as yet unknown. Much remains to be learned about these minute micro-organisms, particularly those, whose habitat happens to be the mucous membrane of the male urethral tract.

It is also striking how many eminent workers, when discussing in the medical literature the problem of N.G.U. are mainly concerned about P.P.L.O., inclusion bodies, and trichomonas vaginalis. The problem of other non-gonococcal organisms is somewhat neglected but on the whole "Bacterial N.G.U." whether original, or post-gonococcal in type plays in my opinion a considerable role in the inflammatory diseases of the male urethra.

My statistical data for seven years (1950-1956) shows separately for each year a distinct numerical superiority of true "Gonococcal Urethritis" over "Non-Specific

Venereal Infections (N.S.V.I). After careful examination and analysis of all cases from the group of "Non-Specific Venereal Infections" (N.S.V.I) and elimination of all kinds of urethritis from the groups of "Balanitis" and "Miscellaneae", the proportion of Abacterial and Bacterial N.G.U. in comparison with true Gonococcal Urethritis rises in the years from 29.8% up to 48.7%, but has not exceeded 50%. The proportion of Bacterial N.G.U. in comparison with Abacterial Urethritis rises in separate years from 21.3% up to 78.8% and the total figures for the seven years period are: 2613 cases of Bacterial N.G.U. and 1339 cases of Abacterial Urethritis.

As previously mentioned I have divided my work into four parts.

In the first part of "Balanitis", in which urethritis plays indirectly or directly a considerable role, it was clearly shown, that only rare cases require a special treatment. This treatment consists usually of one or more of the following: irrigations, sulphonamides, antibiotics and urological, radiological or surgical intervention. Removal of the cause, which may be situated away from or sometimes in the urethra will clear the urethritis completely.

In the second part of "Gonorrhoea mixed with other organisms" it was stressed, that this mixed infection has markedly increased in the last 10 -15 years. This kind of urethritis often affords difficulties in microscopical establishment of the right diagnosis. Cultures, therefore, in these instances are compulsory, and sensitivity tests very essential. In certain cases of mixed infection, especially gonococci and diptheroids, and partially with gonococci and pigmented staphylococci, synergistic combination

of penicillin and sulphonamides, the latter even in small doses, gives good therapeutical results. It seems to be best, therefore, to treat mixed gonorrhoea infection with penicillin combined with sulphonamides or other antibiotics to which the second organisms are sensitive. The selection and administration of the two antibiotics should only be made after cultures and sensitivity tests.

An exception may be the patient, who comes from a considerable distance to the clinic, or a sailor, who next day is going back to sea. Under such circumstances, these patients should receive penicillin injections together with sulphatriad tablets without further investigation. In other cases of mixed infection the patient should receive only injections of penicillin and a few days later after bacteriological results concerning other organisms and their sensitivity are in hand, the other appropriate drug or antibiotic. Waiting for longer than one week after the administration of penicillin, seems to be a loss of time and an unnecessary prolongation of the treatment, because post-gonococcal or rather residual urethritis in mixed cases then appears. By giving penicillin at once we treat the main disease, which is the most important, but by accelerating the further treatment under a week later with special antibiotics or sulphonamides we are not only avoiding the developement of post-gonococcal urethritis with its complications, but also might reduce this type of urethritis or even eliminate it completely.

In urethritis due to gonococci and other organisms it is essential, that we pay equal attention to both types of organisms.

Prostatitis in this mixed group appears much more often than in gonorrhoea alone. In 37 cases of mixed infection prostatitis was found in 7 cases (18.9%) as compared with only 6 cases (5.9%) of prostatitis in 102 cases of gonorrhoea. These findings have been observed by other workers[10] giving similar data. It is also characteristic in some of these cases, that the prostatic gland behaves apparently normally. There is no enlargement and no tenderness, but excreted prostatic specimen shows scattered or clumps of pus cells. In some cases there may be a very mild tenderness or enlargement of the gland. In 3 of the above 7 cases multiple gram positive bacilli together with large numbers of pus cells were found, and in 4 cases only pus cells lying separately or in clumps. Treatment in these cases with prostatitis, in which only pus cells were found in the specimen, consisted of aureomycin capsules (250 mgm four times daily for 5 days). In those with (Gram positive cocci) and pus cells in the secretion-terramycin tablets (250 mgm four times daily for 5 days) were given. This gives satisfactory results, although, sometimes a second course of the antibiotic is required.

In spite of this treatment the prostatic glands in a few rare cases still became slightly tender and enlarged, even, although, a prostatic specimen was unobtainable. The old method of prostatic massage was administered in such instances. Patients after long observation and a satisfactory result obtained from "test of cure" were at last discharged, with injunction to report to the clinic every 6 months for further check-up. This is of special significance in patients over 50 years of age. Only a few of them took our advice.

It would seem advisable, therefore, that the proper public health authorities should issue some decree, which would induce these patients to report to V.D. clinics for subsequent observations. If this could be done, the number of patients requiring prostatectomy might be reduced.

For a correct diagnosis of "Bacterial Non-Gonococcal Urethritis"(B.N.G.U.) discussed in the third part, multiple organisms of at least two different species must be seen on microscopy.

Because of difficulties of correct bacteriological diagnosis in the smears seen under the microscope, cultures and sensitivity tests are not only required, but in the majority of the cases and in all cases of true Bacterial N.G.U. essential. As a rule all cases of true Bacterial N.G.U. require treatment. In some cases, with a short incubation period, a mild urethral discharge in which smears contain: scattered organisms and some pus cells, and with urine slightly hazy in the first glass, or even clear with threads, urethro-vesical irrigations with 1/8000 oxycyanate of mercury are completely curative. In some of these mild cases with more than one species of organisms, urethro-vesical irrigations together with course of sulphonamides (Tabs. Sulphatriad 0.5gm four daily for 4-7 days) is again sufficient to cure the discharge. This treatment should be prescribed immediately to all patients, who can not attend the V,D. clinics frequently and regularly. In other cases, which do not require immediate treatment, cultures and sensitivity tests should and have to be performed before the proper treatment is administered. This treatment may consist of: urethro-vesical irrigations only, or combined treatment with sulphonamides and antibiotics,

including prostatic massages in some cases. On the completion of the treatment tests of cure must be performed. Not every case of this group will require a full test of cure. In some cases it may only be necessary to find, that the urethral discharge has disappeared, that the urine in both glasses are clear, that the curved sound passes the urethral canal, that the serological tests for syphilis at the beginning and the end of the treatment are negative. If only the appearance of the urine in the first glass was changed at the onset and during the treatment, it should not be necessary to investigate the prostatic gland, or if this is done, it should be limited only to the gentle palpation of the gland to find its general consistance, without expressing the prostatic specimen. When the appearance of the urine in both glasses has been changed previously, urethroscope or curved sound and prostatic secretion investigations must be performed.

In all cases of Bacterial N.G.U., who have previously suffered from gonorrhoea, the prostatic gland has to be checked up by microscopical or if necessary cultural investigations. It is astonishing, how often the prostatic gland is involved during Abacterial and Bacterial N.G.U., and how seldom it requires any special treatment. Usually the treatment prescribed: sulphonamides or antibiotics, clears the inflammation of the prostatic gland automatically. Diet, and the general principles of treatment adopted in gonorrhoea, play a large role, and also have to be observed in N.G.U. Prostatic massage should only be done in resistant cases, and usually they are not numerous. All cases with any prostatic involvement, even after successful tests of cure should be advised to report at least twice per year for control investigations. This once again is especially so in patients over 50 years of age.

Infection in Bacterial N.G.U. due to: diphtheroids, bacilli, haemolytic streptococci and staphylococcus aureus, usually show rapid improvement and cure by sulphonamides. Aureomycin therapy seems to have beneficial effect on all staphylococcal organisms, and chloramphenicol on coliform bacilli. Penicillin was not administered in this series of Bacterial N.G.U. (even in positive sensitivity tests) owing to unsatisfactory results and experiences in the past. The same has to be said about streptomycin, the beneficial effect of which is much greater in Abacterial Urethritis.

Each case of true Bacterial N.G.U. has to be very carefully investigated to establish a correct diagnosis. In many instances this diagnosis is much more difficult to make, than in gonorrhoea, and the treatment in many cases is undoubtedly not as easy as in gonorrhoea. Patients must be warned about the complications, which may arise if they do not obey our precautions, and are asked for strict collaboration. If possible, their consorts should be investigated and treated simultaneously. Cleansing of the external meatus before the collection of the specimen is of great importance. A proper diagnosis grounded on clinical observation, microscopical examination, culture and sensitivity test and proper treatment, will cure the patient in a relatively short time and also prevent recurrences. By doing this we can greatly diminish the incidence of urethritis and the consequences in this group.

The term "Abacterial Urethritis" (A.U.) discussed in the fourth part, appears to have different connotations to different authors, but generally there are two diagnostic points:

1) no bacteria found in a stained smear of the exudate and/or negative culture, and

2) no "pathogenic" bacteria noted on stained smear or isolated by culture.

The following have been regarded at one time or another as responsible for the bulk of the cases of abacterial urethritis:

a) Trichomonads.
b) Spirochaetes.
c) Virus.
d) Bacteria - especially in their "L" form.
e) Pleuropneumonia-like Organisms, "P.P.L.O." (Mycoplasma species - mycoplasmata).

In my series of Abacterial Urethritis, all cases of urethritis in which even a few bacteria were found in the smears, were excluded from the group. Cleansing of the external meatus was very carefully done and smears were repeated several times on consecutive days. If other organisms were found in serial stained smears even in small quantities and although they were suspected as possible saprophytes these cases were diagnosed as bacterial and excluded from the abacterial group.

In my series there were 82 completed cases of Abacterial Urethritis. Originally I had 103 cases, but 21 cases became defaulters. Some of theme 21 cases completed the treatment, but the observation period up to the test of cure was not sufficient. The clinical findings, therefore, in my series are based on 103 cases, while the results of treatment must naturally be based on 82 cases. In my series there were 31 cases of the Hecht type and 51 cases of the Waelsh type of urethritis.

Trichomonas vaginalis was found in three cases (3.6%). Cultures of all 3 cases on Stuart carrier medium were negative. It is of interest to note that in all cases of abacterial and bacterial urethritis and in post-gonococcal urethritis culture for Trichomonas vaginalis were negative. In the treatment of this infection Acetarsal seems to be the most effective drug.

Almost all European workers state that Trichomonas vaginalis in the male is one of the causes of N.G.U., and their figures vary between 3 - 10%. Different workers have different techniques of finding the Trichomonas. They may use the traditional classical method of direct examination between slide and coverslip, or they may prefer the method of staining with May-Grünwald-Giemsa. Others use culture and dark-ground. I have used all these methods in each case and I have been successful with only the last one.

Examination for inclusion bodies was done in 103 cases. In each case at least two slides were prepared for each stain: prolonged 1/10 Giemsa and Fuelgen-Schiff. Before accepting the findings as positive, I tried to standardize the appearance of the inclusions; distinct nucleus and cell boundaries, corpuscles stained with Giemsa a definite violet-purple, regular size of the granules, a clearly delimited crescent-shaped group, and a slide without too much debris.

I would stress again the difficulty of finding cells with inclusions. I am rather disturbed by the fact, that even in proven cases only one or two epithelial cells in the whole slide contain inclusion bodies. Slides with even a few micro-organisms were eliminated immediately from investigation for inclusion bodies.

This may be the reason, why my percentage of inclusion bodies is lower than that of certain other workers. If cells which are merely doubtful are regarded as positive, then inclusions may be said to be present in one slide in every four or five.

In, my series of 103 cases prolonged 1/10 Giemsa stained slides revealed inclusion bodies in 11 cases of Waelsh urethritis (10.6%) and in 7 cases of Hecht urethritis (6.8%). In all these cases, which did not show inclusion bodies with Giemsa stain, Fuelgen stain, which shows up the thymonucleic acid in the nuclear stricture and does not stain any kind of bacteria, gave only two positive results (1.9%). Fuelgen stained positive findings in the Waelsh sub-group of urethritis was 5 cases (4.8%) and in Hecht type of urethritis 3 cases (2.9%). The comparitive positive results between the methods of staining percentage is, Giemsa stain 18 cases positive (17.4%) and Fuelgen 8 cases positive (7.7%).

As the Fuelgen method also diminishes my percentage of positive findings for inclusion bodies over the Giemsa stain it permits me to assume the viral origin of the urethritis with greater certainty.

Inclusion bodies cannot be cultured.

Attempts made at cultivation on the fertilised egg so far have given uncertain results. A more satisfactory technique must be developed for the correct interpretation of the presence of the inclusion bodies seen in the urethral tissue of the patients with abacterial urethritis. The Fuelgen method of detecting inclusion bodies is the most accurate of the various stains used and, therefore, should be done in every case.

There have been no cases of urethritis in this series (103 cases) in which Spirocheata pallida or coarse type could be detected. One case of syphilitic balanitis associated with urethral discharge and two cases of phimosis with simultaneous urethritis in which coarse Spirocheatae were found are described in the first part and Appendix. As I lack experience, I cannot discuss "L-forms" in this group of cases.

Perhaps, I should mention briefly two cases (described in the chapter under "inclusion bodies"). These 2 cases were suffering from several recurrences of Waelsh type of urethritis. The first specimen taken from them and stained with gram revealed only pus cells and epithelial cells, Giemsa stained-gave negative results for inclusion bodies. Specimens from them were inserted with sterile precautions into the carrier Stuart media. These revealed multiple staphylococci and diphtheroides bacilli. Gram stained slides taken again a few days later confirmed the presence of these organisms in abundance. There is no question that these patients had had fresh intercourse, or that they had been drinking! It seems to me, that the first microscopical examination was performed at the time, when the organisms were in the "L-form" and, therefore, inaccessible for microscopical observation.

In one of these cases the urethral discharge disappeared spontaneously on the sixteenth day of his first attendance 27 days after the discharge appeared and 41 days after the last sexual intercourse. After 17 days of being completely free from symptoms he suddenly developed a recurrent urethral discharge, which was muco-purulent and quite abundant.

The second case during the "L-stage" had been treated with a course of sulphatriad tablets for 6 days. On the 5th day of the treatment his urethritis had practically disappeared and the patient was symptom free for 23 days, when he reported with recurrent urethral discharge. Before the treatment with sulphonamides in the second case and after a spontaneous disappearance of the urethral discharge in the first patient their prostatic glands were investigated for the first time and did not reveal any abnormalities. Then after the recurrent urethritis several prostatic slides from each case were examined and in Gram stained slides again only pus cells and epithelial cells were found, with no sign of other organisms visible. Giemsa stained slides revealed in both cases inclusion bodies, which were not confirmed by Fuelgen stain.

Culture in the first case was completely sterile, in the second case it showed scattered staphylococci, which were diagnosed as contaminants by the laboratory authorities. Both patients assured me again about not having sexual intercourse. Both were treated with aureomycin capsules and became symptom free for two months, when the tests of cure were performed.

I do not think that frequent collection of the urethral smears and lack of sterility could introduce the organism into the urethra. Bacteriological results of the cultures are against this hypothesis. I also do not think that only one investigation of these patients prostatic glands could have any influence on the presence and appearance of the micro-organisms, especially as their prostatic glands revealed no abnormality. Both of these cases started as typical cases of abacterial urethritis became bacterial and finally reappeared again as abacterial types of urethritis. They were not examined urethroscopically previous to the tests of cure

and so this could not introduce micro-organisms into the urethra. Precautions concerning the cleansing of the external meatus of the urethra were carefully observed. It is also important to add, that cultures for P.P.L.O. performed during the second advent of the abacterial urethritis became negative in both cases, which is rather surprising.

Organism of the P.P. group seems to be organism "per se" and connected neither with bacteria nor with any virus.

Many papers written on this subject showed a clear difference between P.P.L.O. and bacteria in its "L-form", but in spite of this there are still some unanswered questions and doubts.

P.P.L.O. obtained in a high percentage from the uro-genital discharges and from completely healthy males and females seems to be a saprophyte in the human body. It is a saprophyte, which under certain conditions acquires probably a pathogenic feature, and which might evoke some serious inflammation and complication in the urethra. This seriousness is aggravated by rather frequent relapses even without further sexual intercourse. P.P.L.O. in females is more frequent than in males. In male urethritis it is contracted by sexual intercourse. Both partners, if possible, must undertake treatment at the same time.

The tendency to relapses, the chronicity and the complications such as epididymitis and especially prostatitis indicate that treatment in this type of urethritis is essential. Also from the very important social point of view, all these cases must be treated.

The presence of so-called "Amicrobial Urethritis" is much more unpleasant, than an acute attack of Gonorrhoea. The latter can be cleared up fairly rapidly, but the former may persist for a much longer time and can only be cured

by treatment, which is sometimes difficult to endure. The treatment of choice is: Oxytetracyclin (Terramycin) Tetracyclin (Aureomycin), Chloramphenicol and Streptomycin. Penicillin and Sulphonamides do not play the slightest role in the treatment of urethritis in which P.P.L.O. and inclusion bodies have been found.

In some cases of Abacterial Urethritis tablets of Rovamycin (Spiramycin) were used with rather unsatisfactory results. Aureomycin (water soluble) in the form of instillation was used with good results. In the cases treated with Terramycin tablets and Aureomycin capsules a Vitamin 'B' was given at the same time to avoid side reactions such as looseness of the bowels and less often nausea with very good results.

Conclusions.

1) The Investigation of patients with each form of urethritis must be done very carefully, and no distinction can be made between the case of mild, severe, acute or chronic forms of Abacterial or Bacterial N.G.U.

2) Elimination of the causes of urethritis (which are so many and so different) is our principal task, and proper treatment should and must be established, when the cause is obvious to us. "Treat the cause of the urethritis and not the urethritis itself".

3) Cultures and sensitivity tests in all cases of mixed Gonococcal Urethritis, real Bacterial Urethritis and Abacterial are very essential and important, and administration of the proper antibiotic (or antibiotic combined with sulphonamides) following these bacteriological findings will greatly diminish the percentage of these diseases.

4) In Abacterial Urethritis, when methods of investigation are improved the percentage of inclusion bodies and of trichomonads will increase with certainty. The reason, therefore, for such a high percentage of these cases of urethritis remains obscure.

5) P.P.L.O. seems to be, on present investigations, a saprophyte, but under certain conditions might become pathogenic. This pathogenicity increases the seriousness of the type of urethritis produced by P.P.L.O., because of its frequent recurrences and complications such as prostatitis and epididymitis.

In spite of so well differentiated morphology between the P.P.L.O. and the "L-form" of bacteria, both subjects (especially the latter) still require explanations.

In my research I have tried to demonstrate "Brightness and Shadow" in all possible diseases, which have chosen a male urethra for residence. There are still many "Shadows" which require many answers in spite of very careful investigation of each case. The "Brightness" is the careful use of sulphonamides and antibiotics.

VIII. FINAL REMARKS.

From my General Practitioner (G.P.'s) friends I know, that a large majority of them are treating their own patients for all kinds of venereal diseases, particularly all kinds of urethritis. This is all right if general practitioners have sufficient knowledge and experience in these matters. Some general practitioners consult specialists and after receiving advice from them, treat their patients accordingly. It is very obvious that patients having confidence in their panel doctor want first of all some advice from him in venereal diseases as well as in other diseases.

There are several different aspects of a patient's confidence in his panel doctor:

1) entrance to a G.P's surgery does not arouse any suspicions among the patient's family or his friends,

2) patients in general know well, that when they are under treatment in V.D. clinics, they must obey some regulations; they are obliged to attend regularly, if they do not, they may receive letters from V.D. authorities reminding them of their treatment; these letters might get into the hands of the patient's relatives and be a cause of unpleasant misunderstandings,

3) some patients prefer if venereal disease is diagnosed by the panel doctor, that he should also undertake precautions against spreading the disease among the other members of the family,

4) General Practitioners have a greater opportunity to discretely check-up other members of the family with regard to contamination, especially the patients wives.

The big majority of general practitioners in cases of some suspicious ulceration of the genitalia or other parts of the skin and mucous membrane refer their patients to special clinics, but in almost all instances of urethral discharge they treat these patients by themselves.

Very often penicillin is used on clinical grounds only without microscopic confirmation of the diagnosis. This may be satisfactory practically at least, to both parties if the urethritis disappears. In recurrent attacks of urethritis, penicillin and other antibiotcs may be given together or separately on several occasions.

From general practitioners I know again about the complications of patients with urethral discharges namely epididymitis. Some of the G.P.'s are also treating these complicated cases. Investigations of prostatic glands and vesiculo- prostatic secretions are performed only exceptionally and urethroscopic examinations as a rule almost never.

Some of these uncured and complicated cases, (emphasizing points made below), are referred by panel doctors or by themselves to V.D. clinics, because prolongation of the disease has started to worry them.

Antibiotics and especially penicillin is administered today "large manu" too widely, sometimes for insignificant reasons and quite often unnecessarily and in too big doses, which temporarily can mask other more serious diseases such as syphilis. Periodical blood tests are not performed

and so in recent years we have had many cases of Latent Lues discovered accidentally.

These eventualities can be provided against by:

a) close collaboration between G.P's and specialists in all cases, even the most innocent urethritis, until all laboratory findings and the proper diagnosis are established,

b) in some cases treatment will be under the control of G.P.'s entirely, in some cases under specialists control,

c) periodical controls of these G.P.'s treated patients in V.D. clinics mainly for prostatic gland investigations, urethroscopy, blood and final test of cure,

d) occasional meetings of G.P.'s and specialists to discuss these questions.

I would like to underline once more that it is not my intention to undermine or diminish G.P.'s authority. I have the greatest admiration for the G.P.'s enormous task and hard work, but this is the only way, which will allow us to perform properly together our common duties.

To analyse case records at the V.D. clinics is difficult and unsatisfactory. Firstly, I feel that the patients statements are very often open to doubt. They do this sometimes through false shame or fear, occasionally deliberately. Very often at the next visit they take courage and disclose much further and useful information. Secondly, such a huge percentage of patients cease attending before their surveillance is complete. The patient gets well so quickly and so easily (I have in mind gonococcal urethritis), that some

are tempted to run further risk (alcohol, fresh sexual intercourse,) even a few days after the treatment. No longer is the cure worse, than the disease. Quite often patients give false names and addresses, and letters sent to them are returned, and special officers cannot find patients under the addresses given by them. It is a question for the authorities to find a proper solution. My suggestion is, that patients seeking advice in V.D. clinics should have a short letter from their panel doctors with the name and address of the patient.

It is also our duty in the V.D. clinics to inform by letters, with the patient's agreement, the panel doctor about the conditions and treatment of the patient. Then treatment might be conducted by the G.P. and only periodical visits in the V.D. clinic would be necessary.

It is much worse, when patients are told in the V.D. clinics that their urethral discharges are not of gonococcal origin, but of Abacterial or Bacterial N.G.U. This is explained usually to the patients as some "inflammation" or "catharrh" of the urethra.

Only extremely rare cases, even if they are all told of the possible complications of these diseases, will attend regularly unless the disease is really chronic and the patients are tired and feel real discomfort from the discharge.

It is not our intention to frighten the patients, but because our persuasive power is very limited, it is put forward as a suggestion that the proper authorities should class <u>real Bacterial</u> and <u>especially Abacterial Urethritis</u> as diseases requiring compulsory treatment. This could be one of the means of eradicating this disease.

Appendix.

Phimosis.

As a rule urethritis is always present in cases of phimosis with preputial discharge in which gonococci are found. Cases containing non-gonococcal organisms are very rare. In the group of 17 cases of phimosis all except one developed this after sexual intercourse. The phimosis appeared approximately from 4 - 17 days after exposure. Three cases previously had gonorrhoea and 2 cases gonorrhoea and syphilis. Three cases had very mild urethritis with slight prolapse of the mucous membrane of the lips of the meatus. Bacteriological examination of the urethral discharges revealed large numbers of non-specific organisms with pus cells and scanty epithelial cells. One case, a single labourer, aged 27 years, on retraction of the prepuce showed a small erosion situated on the right lip of the external meatus together with some mild urethritis on the 17th day after intercourse. The right inguinal gland was slightly enlarged, but not painful. Dark ground examination revealed Spirochaeta pallida. From the preputial discharge in another 2 cases Spirochaetes (Vincent organisms) have been found without any sign of ulceration or erosion. In 2 cases in which frequent syringing of the preputial sac with a warm solution of 1/10,000 of oxycyanate of mercury and sitz baths failed, dorsal incision was performed.

Condylomata acuminata (venereal warts).

Thirty-one cases of venereal warts have been seen and treated and all of these were more or less complicated with urethritis. Fourteen of the patients denied previous venereal disease. Eight cases had had previous gonorrhoea,

3 balanitis, 3 had been treated successfully some years before for similar warts, 2 had had some urethral discharge a long time ago, which was diagnosed as not gonococcal, and had latent syphilis. The duration of warts varied from few weeks to thirteen months. Five of these cases appeared originally as phimosis. After retraction of the prepuce in three of these 5 cases, multiple condylomata occupied the coronal sulcus and lips of the meatus. In the other 2 cases the glans penis and inner surface of the prepuce were covered with moist cauliflower warts. Several days later when the phimosis had almost subsided after daily subprepucial washes and examination of the patients became easier, it was found that in four cases, the condylomata were situated inside the external meatus. In the fifth case urethroscopy revealed a big solitary wart situated in the fossa navicularis. Thirteen cases (of the 31) showed condylomata situated on the lips of the external meatus, glans penis and prepuce.

In two cases the external meatus was covered with a garland of condylomata. In 3 cases there were only a solitary condyloma on one or both lips of the external meatus. In another 3 cases urethroscopic examination showed scattered condylomata on the mucous membrane of the urethra and bleeding was reported by these patients. In one case urethroscope revealed multiple intra-urethral condylomata situated proximal to fossa navicularis. One case on urethroscopic examination was found to have pedunculated papilloma in the vicinity of the prostatic urethra and he was referred to the urologist. Another peculiar case was seen in which condylomata were situated on the coronal sulcus, and scattered typical lesions of molluscum contagiosum were present on the shaft of the penis, and on the lip of the external meatus. The pearly, grey, rounded papule with a central depression was squeezed and

caseous material found, which revealed typical molluscum bodies under the microscope. This patient was a regular swimmer in the public baths. In the last 2 cases from this series: one had condylomata on the external meatus and around the anal region, and the second had large multiple cauliflower type of condylomata in the anal region, with some moisture and discharge from the rectum.

In my opinion the incidence of genital warts has increased since the advent of sulphonamides and antibiotic therapy. Harkness 1950[2] also noticed this increased incidence of venereal warts. The cause may possibly be the ommission of local treatment (urethro-vesical irrigations) in urethritis.

Treatment of Condylomata.

For meatal and intrameatal warts (2-3 applications per week of) 25% trichloroacetic acid by means of a sharp pointed orange stick, is usually sufficient. If after several applications the warts are still resistant, electric cautery should be used under local anaesthesia. All other warts on the coronal sulcus, prepuce and glans penis respond well to the application of Resin of Podophylin in mineral oil. Kaplan).[3] If podophylin is used, the followimg precautions must be observed: 1) keep the painted areas in the open air for several minutes to allow the podophylin to dry, 2) after eight hours the podophylin should be removed by means of soap and water and the skin carefully dried, 3) the next application if necessary should be repeated after one week.

If these precautions are not observed podophylin might produce severe inflammation of balanitic type. Very good results were obtained using a powder containing 5% podophylin in tannic acid. This is applied to the warts only; whilst

the rest of the normal skin or mucous membrane between the warts must be protected by a thin layer of zinc ointment. After 8 hours the treated parts are cleansed with soap and hot water. The treatment is repeated next day. If further treatment is required it can be repeated in 48 hours. This treatment rarely gives complications but may cause balanitis. If after several applications the warts have not cleared the old treatment of curettage is still very successful. Local anaesthesia is used in the form of Ethyl Chloride spray for scattered warts. Where the warts are multiple and close together local anaesthetic of 2% planocaine with adrenalin is injected. Following currettage a dry dressing of sulphonamide powder is applied. The dressing is changed in 48 hours and the areas are usually healed in 8 - 10 days.

As was mentioned previously a urethritis of varying severity was present in all 31 cases with warts. Attempts in all of these cases to find inclusion bodies in the urethral discharge produced negative results. The concomitant urethritis was not treated but only the cause removed.

Urethroscopic investigations were done in the few cases of intrameatal warts treated with trichloracetic acid or cautery. This was done three weeks after treatment and no abnormalities were found. It might be of interest to mention the following experiment which was performed on 5 cases. (This method is widely used in the Skin Department of the Glasgow Royal Infirmary with some good results). In these 5 patients only a few warts were removed by scraping under ethyl chloride local anaesthesia. The rest of the warts were left untouched. In one patient all the warts disappeared in about 5 weeks. In a second patient all the warts were very much smaller after 4 weeks but this patient did not return for further examination.

In the other 3 patients no change was observed even after three months. The first patient, who was cured was excited and nervous during treatment.

Herpes Genitalis.

Out of 7 cases of herpes genitalis there were only 2 patients in whom the herpetic lesions were situated on the top of the glans penis and on the lips of the external meatus. Only these 2 cases, since they produced some urethritis, will be discussed.

The first case, a motor driver, single, 33 years of age, suffered regularly from "influenza" each spring and autumn. He was first seen in his fourth attack of the common cold. One or two days later a part of the right lower lip was covered with a group of herpetic lesions and simultaneously similar lesions appeared on the glans penis and external meatus. Burning sensation and some pain were felt during micturition. The lesion on the lower lip consisted of one confluent patch of vesicles, those on the top of the glans penis and lips of the meatus were clinically identical and showed no tendency to confluence. There was a slight mucoid urethral discharge. Gram stained slides revealed multiple epithelial cells, many of which were necrotic, scattered pus cells, and a few banal extra-cellular organisms. A smear stained by Giemsa for inclusion bodies was negative, and culture for pleuropneumonia-like organisms yielded no growth. This patient had previously been treated for an allergic skin reaction, although the allergy was never identified. Following local treatment with 3% chloramphenicol ointment the lesions cleared in 24 - 48 hours.

A urethroscopic examination one week later showed nothing relative on the mucous membrane, but on the glans penis some discolouration was still visible. The discharge disappeared completely in about 2 days. When seen 4 months later, there had been no recurrences and he was clinically completely healthy.

The second case, a married man, watchmaker, aged 53, developed a group of the vesicles on the lower lip and chin for the second time in 3 months. A few days later similar skin eruptions appeared on the penis. I did not see this patient during his first attack, but he gave a very accurate description of his disease. There was no connection with casual sexual intercourse. The lesions on the lower lip and chin showed confluent patches covered with crusts and resembled a healing herpes simplex. Penicillin ointment had been given as treatment. The lesions on the penis looked more interesting. There were two patches of typical vesicles, one in the vicinity of the frenulum about the size of a shilling and the other of irregular shape and consisting of typical vesicles situated on both labia and going downwards into the meatus. Before the appearance of the lesions on the penis, the patient felt burning and pain on the surface of the penis. He later developed pain on micturition. A slight milky discharge showed exactly the same picture under the microscope (Gram stained) as in the first case. Again investigations for inclusion bodies and culture for P.P.L.O. were negative and the culture was sterile. The patient was treated with chloramphenicol capsules and vitamin B complex. On the third day all lesions started to heal rapidly. The urethral discharge ceased completely on the fifth day and urethroscopic examination performed a week later showed no abnormality. There were no recurrences during the next year. In both cases herpetic infection was

not of sexual origin.(Esteves and Pinto)[4]

Balanitis Xerotica Obliterans.

There was one patient, who had suffered from the above complaint for 4 years. A miner, married, 51 years of age. Before reporting to the clinic he had had difficulty in micturition with occasional urethral bleeding for the last few weeks. This man had not been circumcised and there was no previous venereal disease. On examination: the prepuce was retractable without any difficulty. On the glans penis there were atrophic, sclerotic, cicatricial patches of ivory colour interspersed with normal tissue. Similar lesions were situated on the lips of the external meatus and there was some scanty, reddish urethral discharge. Smears (Gram stained) revealed: multiple red blood cells, scattered pus cells and epithelial cells (a typical abacterial discharge). Slides stained with Giemsa for inclusion bodies were negative. It was difficult to insert the loop deeper into the urethra, because of pain and bleeding. Only the smallest filiform elastic bougie passed the external meatus. Dilatation at fortnightly intervals and an ointment containing testosterone proprionate was recommended as local application. In two months time in spite of the treatment there was no improvement, but rather deterioration. The patient has had further difficulty in micturition and more frequent bleeding from the urethra. He was subsequently referred to the Urological Clinic.

Erosive and Gangrenous Balanitis.

There were two cases of this condition and both were complicated by urethritis. First case a man, 66 years of age, retired and married, reported to the clinic eight days after casual sexual intercourse. On examination there

was mild oedema of the prepuce and phimosis, but the prepuce was easily retractable. There were two erosions about the size of a sixpence; one situated in the vicinity of sulcus coronaris, and the second one on the right lip of the external meatus producing a mild dirty discharge from the urethra. Both erosions looked suspiciously like syphilis, especially since the inguinal glands were enlarged and slightly painful. Dark Ground examination showed some scattered, coarse spirochaetea, but not spirochaetea pallida. A Gram stained slide from the urethral discharge revealed Gram positive fusiform bacilli, pus cells and red corpuscles. The patient was admitted to hospital and saline dressings were applied. Dark ground examination performed the next day was again negative for S. pallida. It was noticed that both ulcers were larger and deeper. Sulphatriad was prescribed. On the third day the ulcers extended rapidly and formed deep, sloughing excavations. Dark ground for S. pallida was negative. Procaine penicillin 1 mega unit daily was prescribed. Three days later both ulcers showed very marked improvement and regression of inguinal glands was noticed. The discharge from the urethra still present.

The patient, because of his domestic affairs, had to be discharged. Further treatment was continued by his own doctor. He received altogether 6 mega units of procaine penicillin. Blood for W.R. and Kahn (taken before the penicillim treatment commenced) was negative. Seen six months later the blood was still negative and there were firm scars in the places previously ulcerated, especially on the right lip of the external meatus, which showed some deformation compared with the left lip, which had been untouched by the disease. There was no discharge from the urethra and urethroscopic examination showed no abnormality.

The second case: an Indian sailor, 29 years of age, single, developed phimosis five days after casual sexual intercourse. On examination nearly half of the glans penis including the external meatus showed one large and deep ulceration. There was no enlargement of the inguinal glands. Dark ground examination for S. Pallida was negative and only a few coarse spirochaete were found. The discharge from the urethra was examined by Gram stain; Gram positive bacilli and cocci, pus cells and multiple red corpuscles were noted. His V. 15 book revealed, that he was suffering from latent syphilis. In spite of several courses of N.A.B. and penicillin, his W.R. and Kahn tests remained positive. He received 1 mega procaine penicillin daily for seven days and the ulcers healed. Further contact with patient was then lost.

Lichen Planus.

Two cases of Lichen Planus were seen associated with urethritis. These were more or less similar in nature and so only one of these will be described in detail.

A man, 37 years of age, labourer, separated, no recent intercourse, developed 3 weeks before reporting at the clinic, an itching rash, which appeared firstly on the trunk and penis and later on the arms and legs. He simultaneously noticed some discharge from the urethra and it was this, which brought him to the V.D. clinic. The large part of his penis, prepuce and glans including the lips and external meatus, was covered with minute shiny, flat-topped, yellowish-red papules. The first impression was that it was a typical lichen nitidus, but with similar papules covering the trunk, flexor aspects of the joints, wrists and typical mouth lesions. Lichen planus was diagnosed.

The urethral discharge, Gram stained revealed: a mild bacterial urethritis, scattered Gram positive cocci, diphtheroids, pus cells and scanty epithelial cells. Urethroscopical examination showed, milky white papules (the size of a pin-head and even smaller) very similar to those inside the mouth; scattered in the fossa navicularis and extending to the external meatus. Below the fossa navicularis the mucous membrane was normal. A biopsy from the skin of the forearm confirmed the diagnosis of lichen planus. The patient was treated with Sol. Arsenicalis Fowleri. After 3 or 4 weeks of the treatment all the lesions started to fade and itching was less severe. The discharge from the urethra ceased in about 6 weeks without any local treatment. A second urethroscope performed 2 weeks later showed no papular lesions, but only a general redness of the mucous membrane involved previously. At the end of the third month there were only brown pigmented non itching lesions on the trunk, arms, legs and penis.

Lichen Sclerosus et Atrophicus.

There were 2 cases of Lichen Sclerosus et Atrophicus and the following is typical of these.

A man, 57 years of age, taxi driver, complained of a mild urethral discharge for several months. No recent sexual intercourse. On examination: an atrophic, lichenoid patch, whitish in colour was present on the top of the glans penis. It involved the left lip of the external meatus and was the size of a two shilling piece. There was a mild milky discharge from the urethra. Urine was clear with only threads in the first glass. A Gram stained slide showed: scattered Gram positive cocci, some pus cells and epithelial cells. There was some difficulty in passing the urethroscope and, therefore, instrumentation was postponed. A straight sound (No.10) passed. Similar white,

atrophic small patches were situated on the neck and back and very large confluent patches on both wrists. A skin biopsy from the wrist gave a typical picture for lichen sclerosus et atrophicus. After several weeks of regular dilatation of the urethra a urethroscope was passed and revealed: a reddish patch in the fossa navicularis. This was a continuation of the external patch overlapping inwardly from the left lip of the meatus extending for about one inch parallel to the fossa navicularis. The rest of the mucous membrane was healthy and there were no strictures. The patient is still attending the clinic regularly at 6 weekly intervals for dilatation of the urethra. The urethritis is still present with a mild discharge mostly in the morning.

Psoriasis.

There were 2 cases of psoriasis complicated by urethritis. The first case, a miner, 18 years of age, single, developed an acute guttate type of psoriasis 3 weeks before reporting at the clinic. On examination: the entire surface of the body (including scrotum and the glans penis) was covered with typical psoriatic lesions. The few lesions on the glans penis and including some on the lips of the external meatus (a rather unusual distribution) were slightly ulcerated, due probably to the friction of the trousers and dirt in the pit, producing a slight urethral discharge. There was no history of sexual intercourse and no disturbances in micturition. The urine in both glasses was clear, with only some light threads in the first glass. Microscopically Gram stained urethral smear showed the typical picture of exfoliative urethritis. Ung. Paraff. Molle. Flav. externally, and irrigations of the urethra with a very weak solution of oxycyanate of mercury cleared the urethritis in about 3 weeks.

The urethritis worried this patient much more than the skin lesions. In order to settle his nervous distress treatment for urethritis was ordered, otherwise this kind of urethritis does not require treatment.

The second patient: male clerk, 42 years of age, married, had suffered from psoriasis for about 15 years. Some oedema of the penis and urethral discharge brought him to the V.D. clinic. On examination: scattered large lesions of typical psoriasis distributed mostly on the elbows, knees, back of the trunk, scalp and the glans penis. Patient was using for the body (also for his scalp and penis) an ointment containing ½% dioxyanthranol in lanoline. After several applications to the penis developed some erythema and oedema of the glans penis and urethral discharge. Microscopical examination of milky and rather profuse discharge revealed: multiple pus cells, scattered banal organisms, epithelial cells and debris. Urine in the first glass hazy - second glass clear. It was a contact dermatitis of the penis due to the strong ointment, which produced also urethritis. Acid salicyl zinc oil cream healed the contact dermatitis and irrigation of the urethra with 1/10,000 solution of oxycyanate of mercury stopped the urethral discharge in about 2 weeks. Urethroscopy performed 2 weeks later showed no abnormality of the mucous membrane.

Carcimoma of the Penis.

There were 3 cases of carcinoma of the glans penis complicated with urethritis.

The first case: a retired farmer, 71 years of age, appeared in the out-patient skin department in August 1955 suffering from a carcinoma of the glans penis and prepuce of about 8 months duration. The glans penis including the labia of the external meatus was entirely involved with a

fungating mass. There was a mild discharge from the urethra and difficulty in micturition. Gram stained slides of the discharge revealed non-specific organisms, red corpuscles, pus cells and debris. Papanicolau stain for carcinoma cells was negative. An attempted urethroscopy examination failed because of bleeding and probable stricture. The inguinal glands not enlarged. The patient was referred to the Urological Department and biopsy revealed a squamous cell carcinoma. A few days later amputation of the penis was performed and followed by x-ray treatment to the glands. When seen about 6 months later, the man felt very well. The amputated penis had healed very satisfactorily and there was no glandular enlargement.

The second case was seen in the V.D. clinic in November 1955. An engineer, married, 61 years of age, complaining of an urethral discharge of 2 months duration. On examination: both labia and external meatus were red, infiltrated and moist. The infiltration was fairly sharply demarcated. A similar area of infiltration, the size of a shilling, was also present on the glans penis in the vicinity of frenulum. There was no connection between these two lesions and they were separated by perfectly normal tissue. There had been no sexual intercourse and no bleeding. A mild muco-purulent discharge came from the urethra. This contained many pus cells, non-specific organisms, some epithelial cells and a few red cells. Urine: first glass almost clear with some threads, second glass clear. On urethroscopic examination redness and infiltration if the mucous membrane was seen, but did not extend beyond the fossa navicularis. It was sharply demarcated from the rest of the healthy mucous membrane of the urethra. No stricture was present. The prostatic gland was normal, and microscopically the

excretion from the gland was of normal appearance. The patient had suffered from syphilis about 20 years ago and had received treatment with courses of N.A.B., Bismuth and Penicillin. He finally was discharged a few years ago with W.R., Kahn and C.S.F negative. The patient when seen one week later was told, that his blood remained negative, that his discharge from the urethra was not of venereal origin. He was warned, however, that he might have some precancerous disease, and that a biopsy would be of value. He refused to have biopsy and disappeared for several weeks. About 6 weeks later the patient returned. There was no change in the patchy infiltration and redness of the labia and external meatus. The patient complained at that time of some pain and some difficulty in micturition. The urethral discharge was the same, but there was more frequent bleeding from the urethra. The infiltration on the glans penis (in the vicinity of the frenulum) had enlarged and the patch of the labia had also become elongated and nearly confluent with the patch on the frenulum. The surface of this patch was warty, while the patch on the labia still retained a smooth surface. On urethroscopic examination the picture was exactly the same as on the first occasion with no enlargement in the infiltration occupying the fossa navicularis. There was some mild bleeding from the urethra after urethroscopy was performed. A smear from the urethra (Gram stained) revealed multiple red corpuscles, pus cells and non-specific scanty organisms. Scrapings for carcinoma cells stained with Papanicolau were again negative. A biopsy was performed, the specimen being taken from the velvety red patch on the glans penis, and diagnosed:
1) ? Erythroplasia of Queyrat, 2) ? Condylomata acuminata.
The result of the biopsy reported by the pathologist showed that "While precise orientation is impossible there is no evidence of stromal invasion at any part. The appearance

is consistent with the clinical diagnosis of condylomata acuminatum".

When the patient was seen again exactly 4 weeks later the picture had changed completely. The infiltrated patch originally situated in the vicinity of the frenulum had enlarged widely and now occupied almost the whole glans penis. The surface of the infiltration was rough and bleeding. Urethroscopic examination showed exactly the same picture as on two previous occasions. Scrapings for Ca. cells stained with Papanicolau (81) showed a suspicious but not definite picture. There was no enlargement of the inguinal glands. A second biopsy was performed and revealed a very well differentiated squamous celled carcinoma (No: 1698, 30 Jan., '56). The patient had a Radium Mould applied and received 91 hours treatment. On completeion of his treatment he had a brisk reaction, but all induration had gone from the areas and the urethritis had also disappeared. The patient is still under regular observation and control, and to date feels and looks very well. This patient is still a puzzle to me. His primary lesions, one on both lips of the external meatus and in the urethra, the second in the vicinity of the frenulum started according to the patient, almost simultaneously. After several months both these patches became confluent forming one large patch. My own observation showed, that the patch on the labia became gradually elongated and joined the patch below. Urethroscopic examination performed three times did not show any enlargement of the infiltration inside the urethra. The innocent urethral discharge caused the patient to attend the clinic for advice. It is very difficult to establish, if it was a primary squamous carcinoma of the urethra which had spread to the glans penis or vice versa. Primary carcinoma of the urethra is extremely rare. It usually results from direct spread of a carcinoma

of the prostate or penis. The prostatic gland in this case was perfectly healthy and normal. Only a few cases have been recorded in which the primary focus has ocurred in the mucous membrane of one lip or in the fossa navicularis. In this case both lips and fossa navicularis were involved. The exacerbation of the disease with the very sudden enlargement of the lesions on the glans penis while urethroscopic examination performed on three occasions gave each time an exactly similar picture with no enlargement and exacerbation inside the urethra suggest to me, that it was originally a carcinoma of the glans penis. There was no evidence of a pre-existing stricture of the urethra and the patient had not been circumcised. Urethroscopic examination performed nearly one year after completion of treatment showed only: some tightness of the urethra but to date no stricture.

The third case of this group was a man, aged 50, long distance lorry driver, married, was referred to me for examination as ? psoriasis of the glans penis. On examination (in January 1956) slightly raised, red and velvety patches occupied one third of the glans penis and the right lip of the external meatus of the urethra. Duration was 8 to 10 weeks. There had been no extra-marital intercourse. There was a mild discharge from the urethra. No inguinal glands were palpable and he gave no history of venereal and skin diseases. W.R. and Kahn were negative. The urethral discharge stained with: Gram, Giemsa and Papanicolau revealed a non-specific bacterial urethritis. Both urines were clear, with threads in the first glass. On urethroscope: a mild velvety infiltration occupied the right lip and went down into the urethra for about 1½ inches in a narrow line. The provisional diagnosis "Erythroplasia of Queyrat" was established and biopsy performed. The result of the biopsy was " the epithelium over the whole biopsy area shows a diffuse early malignant change. There are numerous mitoses

and bizzare forms, but invasion is minimal. There is also considerable chronic non-specific inflammation". (No. 1699 31 Jan. 1956). The patient received treatment with a Radium Mould. His reaction was not unduly brisk, but complete regression of the neoplasm was anticipated. When seen 2 months later there was no urethral discharge, the patient appeared to be fit and well. There had been no further contact with this patient. (Both these cases Nos. 2 & 3 have been demonstrated in March 1956 - at the North British Dermatological Society in the Skin Department of Glasgow Royal Infirmary).

Strictures.

The incidence of urethral strictures in males has fallen steadily in the last 15 years. This is attributed largely to the sulphonamides and antibiotics. There, however, remains a fairly large number of cases of strictures dating from the pre-sulphonamide era and these still attend for regular dilatations by bougies. These cases resulted from the use of too strong local irrigations e.g. silver nitrate (64 grains to the ounce), mercury perchloride (1/240), potassium permanganate (1/480). These patients as a rule have urethral discharges, straining, frequency, occasional dysuria and incontinence depending on the severity of the strictures. There were 3 patiants with strictures, whose urethral discharge brought them to V.D. clinics to seek advice.

The first case seen in April 1955 was a junior officer in the Merchant Navy, single, 31 years of age, with no history of venereal disease in the past. About 5 years ago when playing football in India, he was accidentally kicked in the genitalia and was taken to hospital, because of bleeding from the urethra. Eight days later he was discharged with no complaints. Three and a half years

later he noticed some straining, frequency in micturition and a continual mild urethral discharge. He was treated for a long time in different V.D. clinics at home and abroad for non-specific urethritis. He received various antibiotics, sulphonamides and irrigations. On examination there was a scanty urethral mucoid discharge; Gram stained slides revealed few pus cells and epithelial cells, scattered Gram positive cocci and diphtheroides. First glass of urine almost clear with threads, second glass clear. Prostatic gland - normal. On urethroscopic examination, about 2½ inches below the external meatus a very hard and tight stricture was found. Only an elastic filiform bougie passed with difficulty and because of bleeding, further examination was postponed. When seen 3 weeks later another filiform bougie was tried; it passed the first stricture and another stricture was discovered just in the vicinity of the membranaceous part of the urethra. The patient still attends very regularly for treatment by means of bougies. Now a curved bougie No. 16/20 can pass the urethra with only slight difficulty causing no discomfort in micturition and no bleeding. There is still an irregular mild urethral discharge. The striking features in this case is the long period between the accident and the appearance of urethritis. The patient's statement, that there was no venereal diseases in the past and no intercourse between the accident and the onset of the urethritis must be accepted (cum grano salis).

The second case, a sailor, single, 32 years of age was seen in the V.D. clinic in May 1955. Two years before he developed an urethral discharge, while in Cairo. He was treated at sea by one of his officers (non-medical) with some tablets. The patient, an intelligent man, stated, that his urethral discharge associated with frequency of micturition and pain appeared on the fourth day after

sexual intercourse. At the same time he developed several small ulcers on the preputial opening and the coronal sulcus, and some pain and enlargement in the right groin. On the first day of the treatment with tablets (probably sulphonamide because they are very widely administered by naval officers when doctors are not available) the patient's micturition became very painful and he noticed some blood in the urine. This settled in a few days, and the ulcers healed in about 5 days. He was on three tablets daily for 10 days. After returning to this country, blood was taken on two occasions and was negative. He had no complaints. Exactly 2 years later he developed some straining and later frequency of micturition and an urethral discharge. According to the patient there had been no sexual intercourse since his last "bad" experience. On examination there was a mild mucoid discharge, microscopically only some pus cells and epithelial cells and no organisms seen. Prostatic gland normal, specimen normal. On urethroscope: a stricture was found in the first third of the anterior urethra. A gum-elastic No. 6 bougie passed the stricture. The patient is now receiving curved bougies at regular intervals and now a No. 10/14 is passing the stricture quite easily. There are the following suppositions concerning this patient's urethral stricture:

1) An intraurethral chancroid contracted with gonorrhoea.

2) An intraurethral chancroid contracted with N.G.U.

3) Stricture following gonorrhoea alone.

Against the third supposition is, that the time lapse is too short for a stricture to be produced. In the vicinity of the frenulum there was still a slight scar, which could be residum of post chancroid ulceration.

The third case, a business-man, divorced, 42 years of age had been treated privately for three years for an urethral discharge. On examination there was a scanty milky discharge. A smear - Gram stained showed a typical abacterial picture with only pus cells and epithelial cells. Giemsa stain revealed inclusion bodies. Culture on special medium - negative. Prostatic gland normal. Specimen microscopically normal. The patient had contracted gonorrhoea eight years before and was treated with penicillin injections. Urethroscopically a stricture was found in the anterior urethra about 4 cms. below the fossa navicularis. The patient started treatment by means of bougies and the last one which passed easily was No. 12/16. In this patient there are two possibilities in the developement of this urethral stricture:

1) previously contracted gonorrhoea,

2) stricture following bacterial urethritis of venereal origin.

The patient was treated with aureomycin capsules (250 mgm each four daily for 6 days). The urethral discharge disappeared during the treatment, but recurred 3 weeks later in a much milder form. The patient is still attending the V.D. clinic. In last 7 months of 1956 there have been another 3 cases referred to me suffering from chronic bacterial urethritis. They have been treated previously with: sulphonamide tablets, different antibiotics and urethral washings with only temporary improvement. In all 3 cases multiple strictures have been found and regular treatment with bougies has resulted in good improvement in all.

Keratodermia Blenorrhagica.

The following paragraph refers to all those cases of K.B., which I have seen during the past twenty-five years

both, here and abroad. The reason for including this disease will be mentioned later. Altogether I have seen 11 cases of K.B. Seven of them I observed in Poland during 1931-39, and despite the lapse of time I have still these cases fresh in my mind. The other 4 cases have been observed as follows: one in 1940 in Norway, and 3 cases in this country (1942-1954). The 7 cases observed in Poland were male patients, suffering from mono or polyarthritis, urethritis, and occasionally also from conjunctivitis due to freshly or previously contracted gonorrhoea. In 6 cases K.B. ocurred on the soles, and only in one case on the soles and palms. Only 2 of these cases were treated with the precursors of sulphonamides (Uliron and Dagenan) in 1937. Five cases before this era, were treated with the treatment available at that time. In all these 7 cases gonococci were found in the urethral discharges on microscopy and on cultures on admission and later during the appearance of the complications. The time between the contraction of gonorrhoea and the appearance of complications (arthritis, conjunctivitis and K.B.) varied from 3 weeks up to 2 months approximately.

The case in Norway in 1940 concerned a young soldier, 19 years of age with an acute arthritis of both shoulders and the right knee, urethral discharge, conjunctivitis and K.B. on both soles. This patient on a ship sailing from France to Norway, complained of an urethral discharge and painful micturition eight days after sexual intercourse in France. He was treated with sulphonamide tablets. In spite of treatment three weeks later appeared the complications mentioned above. It has to be stated, that the urethral discharge was not examined microscopically because of the lack of a microscope. Clinically the diagnosis was that of a typical gonococcal urethritis with all the complications mentioned above. The patient was sent to the

military hospital on Lofotten Islands and contact with him was lost.

The second case, also a young soldier from the allied forces was observed in 1942 in Gartloch Military Hospital. On the seventh day after sexual intercourse he developed a urethral discharge. Microscopically: gonococci positive. At the end of the second week, when patient was under treatment with sulphonamides he developed arthritis of both ankles and the right knee; later a mild transient bilateral conjunctivitis developed, still some urethritis and in the third week K.B., which affected only the right sole. His left sole, however, was covered with typical parakeratotic nodules.

The third case was a man, 25 years of age, who was admitted in the early autumn in 1948 to the medical wards of Glasgow Royal Infirmary with the symptoms of acute polyarthritis of a few weeks duration. K.B. appeared a few days after admission on both palms and soles. The patient stated that about 6 weeks before admission he had been treated for gonorrhoea. Urethral discharge was mild and microscopically showed only some non-specific bacteria, the conjunctivitis, however, was rather severe.

The fourth case was a male, 39 years of age, married, who appeared in the out-patient Skin Department of Glasgow Royal Infirmary on 3rd June 1954. On examination he had bilateral conjunctivitis, urethral discharge, acute inflammation of the left ankle and K.B. on both soles. Several smears from the urethra and conjunctivae stained with Gram and Giemsa were negative for bacteria and inclusion bodies, except for a few scattered saprophytes. Only some Gram positive cocci with scattered pus cells were obtained from scraping of the parakeratotic nodules.

The patient denied a recent sexual intercourse. His prostate investigated a few days later after admission, showed some enlargement and tenderness on the right side of the gland. The specimen obtained from the prostatic gland revealed multiple pus cells and no other organisms. Giemsa stain for inclusion bodies was negative. At this time patient confessed that, on 25th May he had attended Black Street V.D. clinic suffering from some urethral discharge and inflammation of the prepuce, which he contracted 6 days after a sexual intercourse. He had been diagnosed at the clinic as a case of "ulcerative balanitis". No details of microscopic examinations were available. Patient received at the clinic 1 mega unit procaine penicillin daily for three successive days. From the records it was discovered, that this patient had been treated for gonorrhoea in 1951, and that a few months later he had been treated for Reiter's disease in Belvidere Hospital. At that time he was suffering from: urethritis and arthritis of the right knee and left ankle.

These details are given here, because it is my first case of K.B. not associated with previous gonorrhoea and secondly, that "old song" was confirmed - never trust V.D. patients. I would like to underline how difficult it is to obtain real and true information from V.D. patients. Another problem now arises. Was this a first attack of Reiter's syndrome or merely a recurrence of the disease, the first attack being 5 years before? In my opinion it was a recurrence!.

This patient later developed an acute inflammation of right knee, left shoulder and right hip. The urethritis and conjunctivitis were rather mild. A biopsy of the skin lesion showed changes consistent with the diagnosis of K.B., and culture of the pus from the lesions yielded

a coagulase positive staphylococcus aureus in pure growth. Organisms morphologically identical pleuropneumonia-like organisms (P.P.L.O) were seen on urethral smears, but attempted cultivation was unsuccessful. Courses of different antibiotics were administered:- penicillin, aureomycin, chloramphenicol, as well as anthisan and butasolidin, but the condition seemed to run its own course. The skin lesions were treated for one week with 3% aureomycin ointment with good results.

The majority of venereologists are of the opinion, that Keratodermia Blenorrhagica is a blood-born manifestation of a bacterial urethritis. When K.B. occurs in association with gonococcal urethritis, there is always a mixed infection, but gonococcus plays no part in the appearance of the eruption. Though this may be coincidence in my experience all 11 cases of K.B. have had gonococcal urethritis, freshly contracted or in the past (except the one case in whom war difficulties did not permit microscopical examination, but in whom the clinical manifestations were very similar to those of gonorrhoea).

Reiter's Disease.

Four cases of Reiter's disease have been observed. Two of them having their first attack, two their second attack (one - four years ago, one seven years ago). All men, aged 27 - 49, two single, one widower, one married. Only two patients have had all manifestations attributed to R.D. - namely: urethritis, arthritis and conjunctivitis. One case was during the first attack and the other during a recurrence 7 years after the initial attack. The remaining 2 cases have had only: urethritis and polyarthritis with mild balanitis. Only the one recurrent case (first attack 7 years ago) confessed, that he had had gonorrhoea in 1944 during the war. The remaining 3 cases denied having venereal

diseases - no dysentery in all four cases. In all 4 cases as a first symptom there appeared urethritis, later on followed in one week's time by arthritis. In one case conjunctivitis appeared bilaterally, and in an acute form; in one case conjunctivitis was very mild and transient. It is difficult to judge how many of the clinical manifestations are necessary to make a proper diagnosis of R.D. In 2 cases in which the full triad of symptoms was present, the diagnosis was obvious. In another 2 cases in which only urethritis and polyarthritis were present, the polyarthritis indicated the diagnosis.

To establish a diagnosis of R.D. the presence of urethritis and polyarthritis is necessary. Monoarthritis with urethritis causes doubts about the diagnosis. However, the persistence of these two symptoms despite treatment and the later involvement of the other joints clarifies the doubts. Conjunctivitis in this disease is the least important manifestation of the syndrome. In all 4 cases the urethral smear Gram stained, revealed a typical abacterial picture. Giemsa stain (prolonged) showed inclusion bodies only in one case (first attack). Conjunctival smears stained with Giemsa for inclusion bodies were negative, all cultures on ordinary media were sterile. Only in 1 case (first attack) urethroscopy was performed (mild urethral discharge of 10 days duration with painful inflammation of both ankles and the right knee joints). Urethroscopy revealed: some excrescences resembling cobble-stones, situated on the roof and lateral walls of the anterior urethra. In 3 remaining cases urethroscopy was postponed, because of acute course of the symptoms.

The following treatment was administered: aureomycin, terramycin, streptomycin, sulphathiazole and antihistamines.

Only 1 case (first attack seven years ago) responded very rapidly to terramycin (four tablets - 250mgm each daily for 6 days) on the fourth day of the treatment. He became symptom free on the first day after the completion of the treatment. Urethritis and conjunctivitis disappeared entirely though he still had some oedema and inflammatiom of the joints, which automatically regressed on the 12th day. Under observation for about 4 months - no recurrences. The other 3 cases showed only temporary improvement during the treatment and they ran their own course. All symptoms subsided from 4 - 5½ months from the beginning of the disease. No complications such as epididymitis or prostatitis have been noticed.

Stevens-Johnson Syndrome.

As many writers have already suggested Stevens-Johnson Syndrome is a variant of bullous erythema multiforme. The characteristic features of this syndrome are: a rash, stomatitis, ophthalmia, urethritis and fever (of varying severity). The course of the disease may be a few days or many weeks. The eye lesions are the most serious features of the syndrome, as they frequently lead to permanent blindness. They may consist of simple conjunctivitis, iritis, iridiocyclitis or panophthalmia. Urethritis is nearly always present and is seldom severe. The appearance of the early lesions resembled typical erythema multiforme. Stomatitis varies from mild inflammatory lesions to severe ulcerating lesions. Occasionally S-J syndrome may be associated with arthritis, and then it may be difficult to distinguish it from Reiter's Disease. The cause of the condition is unknown.

I have seen 3 cases of S-J syndrome at the Skin Department of Glasgow Royal Infirmary. The first case:

a boy 3½ years old was first seen in September 1948. Six weeks earlier he had developed a left sided cervical swelling, which had been diagnosed as mumps. His mother and 16 year old sister had had "quinsy" throats 3 weeks before his admission to hospital.(5) On admission: there was circumoral erythema and blood stained crusts on the lips; inside the mouth there were circular whitish aphtous ulcers on the cheeks, palate and tongue, bilateral blepharitis and conjunctivitis with a purulent exudate was also present. The skin on the chest wall and upper abdomen showed a scattered papulo-follicular eruption and on the upper limbs scattered vesicles and bullae. Similar lesions were present on both legs; a purulent discharge from two small preputial ulcers and a mild discharge from the urethra was present. He complained of painful hands and feet. Temperature was 99.6°F. This boy had received two intramuscular injections of penicillin before his admission to hospital. Treatment: 20,000 oxford units of penicillin were given orally every 2 hours and penicillin was also instilled into the eyes. Soft paraffin was applied to the skin and the mouth swabbed twice daily with glycerine and borax. At the end of the third week the eye lesions, the ulcers in the mouth and the preputial ulcers were almost healed. The skin lesions started to heal slowly after 4 weeks. The patient was discharged 63 days after admission.

Swabs taken from the throat, conjunctivae and preputial ulcers all give a positive culture of staphylococcus aureus. Fluid from one bulla was sterile. The treatment seemed to have little effect on the general course of the disease, especially on the acute phase which lasted about 3 weeks. It was of great value in one respect, namely, in controlling serious eye complications. Today with newer antibiotics at our disposal it is easier to treat these diseases.

The second case a man, 20 years of age, presented in 1951 with the typical manifestations of the S-J syndrome namely skin lesions, stomatitis, ophthalmia and urethritis. The disease had been present for several days before admission. On admission: temperature 103°F. Swabs taken from the mouth, conjunctiva and urethra revealed positive cultures of staphylococcus aureus, sensitive to aureomycin and penicillin. Giemsa stained slides - negative for inclusion bodies. Treatment: with aureomycin capsules 250 mgm each - 2 every 4 hours for 2 days and then 1 6 hourly for another 3 days gave a very satisfactory result. The urethritis and conjunctivitis had disappeared at the end of the treatment, although the mouth lesions took some time to settle down. There were no recurrences of the skin lesions observed.

The third case, a man, 56 years of age, married, suddenly developed very severe mouth lesions with scattered eruptions of erythema multiforme on the arms and legs. This was associated with a mild conjunctivitis and urethral discharge. There had been severe pain on micturitition for several days before the appearance of urethral discharge. This patient had suffered from prostatitis for several years. From the conjunctiva and urethral discharge, inclusion bodies were found in Giemsa stained slides. No cultures were attempted. A course of terramycin tablets resulted in a great improvement in all symptoms. On the fifth day all symptoms had disappeared completely. Four days later a mild recurrence of stomatitis and balanitis again appeared, but not conjunctivitis nor fresh skin lesions were observed. A second identical course of terramycin tablets was administered, and compresses of weak solution of oxycyanate of mercury were applied locally for the balanitis. At the end of the second week all signs and symptoms had settled down.completely, except

some difficulty in micturition. At the end of the third week a prostatectomy was performed with very satisfactory results up to date.

Cowperitis.

A young man, single, 22 years of age, was seen in 1954, when he contracted gonorrhoea. He had a mixed infection with gonococcal and non-gonococcal urethritis. He was treated with procaine penicillin 300,000 units and 5gm. of sulphatriad. Because of his work (tunnel worker in the North of Scotland) he could not attend the clinic regularly. The treatment which he received caused a marked decrease of his discharge, but never cleared it completely. The patient stated that, half an hour after he left the clinic he vomited. (This was probably due to the sulphonamide tablets). He returned 5 weeks later with some urethral discharge and denied sexual intercourse or drinking. On examination there was a mild milky urethral discharge; first glass of urine almost clear with threads, second glass clear. Gram stained slides revealed: scanty pus cells, Gram positive cocci and diphtheroids and a few epithelial cells. The patient complained of some pain in the perineal region, especially when sitting down or rising. There was no frequency in micturition, but some pain at the end of micturition. On urethroscope- no abnormalities. Prostatic gland normal also vesiculae seminales. Both Cowper's glands were enlarged, palpable and slightly tender. The patient was treated with streptomycin injections - 1 gm. daily for 5 days. He was seen again 2 weeks after completion of the treatment. He had no complaints, no urethral discharge and no pain on micturition. In another two weeks rectal examination revealed only very mild tenderness in the right Cowper gland. No further treatment was given and two months later tests of cure were completely negative.

The second case, a sailor, seen also in 1954, 27 years of age, single, was treated on the ship for some urethral discharge, which he contracted in Spain. Received about 60 tablets (? probably sulphonamides) from his non-medical ships officer. When seen about 4 weeks later he had a moderate muco-purulent discharge. Gram stained slide showed: numerous Gram positive cocci (some in chains), pus cells and epithelial cells; first glass of urine hazy with threads, second glass clear. Patient complained of pain in perineal region especially at the end of micturition. On urethroscope only some redness of the mucous membrane, prostatic gland normal, the right Cowper gland was tender and enlarged. Patient received streptomycin injections 1 gm. daily for 4 days and when seen 3 weeks later he was well and fit. In another 6 weeks test of cure revealed negative results, but the Cowper gland still remained palpable.

Chronic Furunculosis (Boils)

Patient, 50 years of age, joiner, widower, had suffered from Chronic Furunculosis for nearly 1½ years. He was treated by his panel doctor with two courses of procaine penicillin injections and one course of intensive treatment with sulphatriad tablets with only temporary relief. He was seen in out-patient Skin Department of the Royal Infirmary in September 1952. On examination: scattered boils mostly on the neck with multiple scars on the neck and buttocks. He had a mild milky urethral discharge of long duration with occasional burning sensations in the urethra, but no difficulties in micturition. Gram stained slides revealed: scanty Gram positive cocci, pus cells and a few epithelial cells. On culture - staphylococcus aureus. Urine: 1st glass clear with some light threads, second glass clear, no glycosuria was present. Investigation of prostatic gland showed, that the right lobe

of the gland was slightly tender; prostatic specimen showed: pus cells - scattered and some in clumps. The patient had gonorrhoea 12 years ago. A swab taken from the boil and vaccine prepared; meantime local treatment with 3% aureomycin ointment was prescribed. No treatment was given for the urethritis and prostatitis only abstention from sexual intercourse was indicated. When seen in three months time after completion of vaccine treatment, there was no discharge from the urethra, both glasses of urine clear, prostatic gland slightly palpable on the right side, secretion of the gland not available on two occasions at 3 weekly intervals. On urethroscope: no abnormalities. The patient has been discharged and cured. This case illustrates a urethritis secondary to chronic furunculosis. In my opinion the fact that this patient had suffered from gonorrhoea 12 years previously played no part in the production of the urethritis.

Periurethral Abscess.

Patient 23 years of age, single, Negro, railway worker, had had gonorrhoea three times previously. His last attack was 6 weeks before reporting to the V.D. clinic in August 1954. On examination: he had an acute periurethral abscess associated with urethral discharge, both conditions had been present for about 5 to 6 days. According to patient's statement there had been no sexual intercourse since the contraction of the last gonococcal infection. No enlargement of inguinal glands. Some frequency of micturition and pain mostly at the end of micturition. Gram stained slides revealed: Gram positive cocci, scattered diphtheroides and pus cells. Treatment: one mega procaine penicillin daily for 5 days. A marked improvement was noticed during the treatment. In 2 weeks the periurethral abscess had disappeared completely. There was still a morning discharge

from the urethra showing scattered pus cells and a few Gram positive cocci, urine clear. In another 2 weeks urethroscopy was performed and revealed an "urethroscopic stricture" in the anterior urethra 2½ inches from the fossa navicularis. Prostatic gland normal, secretion of the gland normal. Urethral washes with 1/8000 oxycyanate of mercury every second day for 10 days completely eliminated the urethritis. Test of cure performed in another 6 weeks were negative. There had been no relapse of the urethritis when seen 2 months later.

IX. ACKNOWLEDGEMENTS.

My thanks are due to many persons.

I am especially indebted to Professor G.M. Wishart for his constant encouragement and advice and for his suggestion to change the title of my thesis from "Abacterial Urethritis" to "Urethritis".

To Professor G.L. Montgomery and to his successor Professor T. Symington. I would proffer thanks for much helpful supervision and invaluable advice.

Dr. J.C. Ives and Mr. W. McCormack have given a great deal of technical advice on the bacteriological side and I am very grateful to them.

Dr. P. Pullar has given much advice and help in the subject of inclusion bodies, and Miss J. Kenyon in the technical side and I thank them for this.

I am indebted to Mr. P. Elliott for photographs.

I should also like to thank Dr. G. Harvey and Dr. A. McPhater for access to their clinical material.

X. References.

1. Year Book of Dermatology and Syphilology 1953 - 1954
   Problem of Syphilitic balanitis.

2. HARKNESS, A.H. Non gonococcal urethritis.
   Edinburgh, (1950). 172.

3. KAPLAN, J.W. (1942). Condylomata acuminata.
   New Orleans Med. Surg. J., 94. 388.

4. INVENAL ESTEVES and MANUEL R. PINTO (1952).
   Herpetic urethritis. Brit. J. vener. 28.205.

5. J.O'D. ALEXANDER. (1949). Stevens-Johnson Syndrome:
   Report of a case. Glasgow Medical Journal.
   Vol. 30, pp. 455-457.

6. MARSHALL James, "The Venereal Diseases".
   A manual for Practitioners and Students. London 1944.

7. PELOUZE, P.S. Gonorrhoea in the male and female.
   Philadelphia and London, 1941.

8. LEES DAVID,(1931). Diagnosis and treatment of Venereal
   Diseases. (Edinburgh, Eg. S. Livingstone).

9. McDONALD,J.E.R., Biology and treatment of Venereal
   Diseases. London, 1915.

10. BOURGAULT DU' COUDRAY, F.C., Brit. Med. Journal.
    1947, Oct. 25, p. 651.

11. VON WAHL, A., 1911. Die Erreger der chronishen urethritis.
    Dtsch. med. Wschr., 37. 1118.

12. STUART, R.D. (1946). Centralised gonococcus culture
    for dispersed clinics. Glasgow med. J., 27. 131.

13. MARY MOFFETT, JEAN L. YOUNG and R.D. STUART.
    Brit.Med. Journal. August 28, 1948, vol.ii p.421.

14. De BORD, G.G. (1943). J.Lab.Clin.Med., 28, 710

15. JAWETZ, E. and GUNNISON, J.B., 1952 a.
Antibiotic and chemother.2. 243.

16. GARROD, L.P., Combined chemotherapy in bacterial infections. Brit.Med.Journal, May 1953.

17. HOBBY, GLADYS, L., and DAWSON, M.H., 1946.
J. Bact. 51. 447.

18. JAWETZ, E. and GUNNISON, J.B. (1952b).
J. Amer.med. Ass. 150. 693.

19. WILLIS, V.N.B., Urethritis in the male.
The Med. J. of Australia. Sept. 26.1942. p. 294.

20. COOPER BOOTH J., The prophylaxix and treatment of Venereal diseases at a public clinic.
Med. J. of Australia. 26.Sept. 1942. p. 292.

21. GIBSON, N., Control of Venereal Diseases in the Army.
The Med. J. of Australia. Sept. 26. 1942. p. 290.

221. HARKNESS, A.H., Non gonococcal urethritis.
Brit. J. Vener. Dis., 9. 173. 1933.

23. HARKNESS, A.H., Reiter's Disease. Brit. Med. Journal.
1. 72. 1947.

24. HARKNESS, A.H., Pathology of gonorrhoea.
Brit. J. Vener. Dis., 24. 137. 1948.

25. TOPLEY and WILSON, S., Principles of Bacteriology and Immunity, 3rd Ed. I. 939 - 948. 1947.

26. The Lancet, 2. Oct. 1954. Non-gonococcal urethritis.

27. AMBROSE SAMUEL, S., and TAYLOR WILLIAM, W.,
A Study of the etiology, epidemiology and therapeusis of non-gonococcal urethritis.
Amer.J.of Syph. Gon. and Vener. Diseases. Nov.1953.

28. AMBROSE SAMUEL, S., Pathogenesis of non-gonococcal urethritis.. WHO/VDT/131. 16. Sept. 1954.

29. SOREL,C.L. Survey of Trichomonas Vaginalis in men - critical examination of the methods used for detection of the parasite - description of techniques. WHO/VDT/124. 21 July, 1954

30. COUTTS,W.E., et al. Trichomonas Vaginalis. Infection in the Male, Brit.Med. Journal. Oct.8. p.885.1955.

31. LYDON,F.L. Trichomonas Vaginalis Infection in the Male. Brit.Med. Journal. Dec.10. 1955. p. 1447.

32. BUSHBY,S.R.M., CATTERALL, R.D., and WILLIAMSON MARY (1955). Brit. Med. Journal, V.1. 78-80. (BULL.HYG., 1955, 310,) An Amido-Nitrothiazole for Trichomoniasis.

33. WHITTINGTON, J., Trichomonas Vaginalis Infection in the Male. Brit. Med. Journal. Nov.12. 1955. p.1209.

34. BOURNE, A., Trichomonas Vaginalis. Brit.Med. Journal. Jan. 22, 1955. p. 226.

35. CZEKALOWSKI, J.W., and McLEOD, J.W., Detailed description of a Leptospira obtained in pure cultures from the urine in a case of abacterial cystitis. The J. of Path. and Bact., Jan.1954.p.43-50.

36. KLIENEBERGER, E. The natural ocurrence of P.P.L.O. in apparent symbiosis with Streptobacillus moniliformis and other bacteria. J. Path. Bact., 40: 93-105, 1935.

37. RUITER, M., and WENTHOLT, H., Isolation of pleuro-pneumonia-like organisms (P.P.L.O) in primary fuso-spirochaetal gangrene of the penis. J. Invest. Dermat., 15: 301-304, 1950

38. KLIENEBERGER, E. Further studies on Streptobacillus moniliformis and its symbiont. J. Path. Bact., 42: 587-598,1936.

39. KLIENEBERGER, E. The P.P.L.O: further comparative studies and a descriptive account of recently discovered types. J. HYG.CAMB. 40: 204-222.1940.

40. SABIN, A.B., The filtrable micro-organisms of the P.P. group. Bact. Reviews, 5: 1-66, 1941.

41. KLIENEBERGER, E. The colonial development of the pleuropneumonia-and agalactia on serum-agar and variations of the morphology under different conditions of growths. J. Path.Bact., 39: 409-420. 1934.

42. KLIENEBERGER, E., Some new observations bearing on the nature of the P.P.L.O., known as "L1", associated with Streptobacillus moniliformis.

43. KLIENEBERGER,E., and SMILES, J., Some new observations on the development cycle of the organism of bovine pleuropneumonia and related microbs. J. HYG.CAMB., 42: 110-123, 1942.

44. DIENES,L., Cultivation of P.P.L.O. from female genital organs. PROC.SOC.EXPER.BIOL.MED. 44: 468-469.1940.

45. SMITH, W.E., Isolation of P.P.L.O. from man. J. Bact. 43: 83, 1942.

46. DIENES,L., and SMITH, W.E., Relationship of P.P.L(L) organisms to infections of human genital tract. PROC.SOC.EXPER.BIOL.MED. 50:90, 1942.

47. BEVERIDGE, W.T.B., Isolation of P.P.L.O. from the male urethra (quoted from Klieneberger L (27) Med.J. Aust. 2: 479, 1943.

48. KLIENEBERGER,E., P.P.L.O. of diverse provenance: Some results on an enquiry into methods of differentiation, J.HYG.CAMB. 38:458-476, 1938.

49. KLIENEBERGER, E., and STEABBEN,D.B., On a P.P.L.O. in lung lesions in rats, with notes of the clinical and pathological features of the underlying condition. J.HYG.CAMB. 37: 143-152, 1937.

50. FINDLAY,G.M., et al: Rolling disease. New syndrome in mice associated with a P.P.L.O. Lancet, 235:1511-1513. 1938.

51. LAIDLAW, P.P., and ELFORD, W.J., A new group of filterable organisms. Proc.Roy.Soc.120:292-303.1936.

52. KLIENEBERGER-NOBEL, E., P.P.L.O. in the human vagina. LANCET. 2:46-47,1945.

53. SALAMAN, M.H., Non-specific genital infections. The isolation of organisms of the P.P. group from the genital tract and their relation to the gonococcus. BRIT.J.VENER.DIS., 22: 47-54. 1946.

54. HERRICK,V.W., and EATON, M.D., An unidentified P.P.L.O. isolated during passages in chick embryo. J.BACT.50:47-55. 1945.

55. KLIENEBERGER, E., and STEABBEN, D.B., On the association of the P.P.L.O. - L3 with bronchiectasis lesions in rats. J.HYG.CAMB. 36:122-128. 1938

56. EDWARD,D.G.ff. The P.P. group of organisms; a review together with some new observations. J.GEN.MICROBIOL. 1954. 10. 27-64.

57. KLIENEBERGER-NOBEL, E., Micro-organisms of the P.P. group. BIOL. REV. 1954. 29. 154-184.

58. RUITER,M., and WENTHOLT, H.M.M., The occurence of a pleuro-pneumonia-like organism in fuso-spirillary infections of the human genital mucosa. J. INVEST.DERMAT. 18:313, 1952.

59. RUITER, M., and WENTHOLT, H.M.M., Isolation of a P.P.L.O. (G. Strain) in a case of fusospirillary vulvovaginitis.
ACTA.DERM-VENEROL. 33 - 123, 1953.

60. RUITER, M., and WENTHOLT,H.M.M., Incidence, significance and bacteriological features of P.P.L.O. in a number of pathological conditions of the human genito-urinary tract.
ACTA. DERM-VENEROL. 33:-130, 1953.

61. NICOL, C.S., and EDWARD, D.G., Role of organisms of the P.P. group in human genital infections.
BRIT.J.VENER.DIS., 29:141, 1953.

62. SHEPARD MAURICE, C., Some preliminary observations: pleuropneumonia-like organisms in men with non-gonococcal urethritis at camp LEJEUNE, North Carolina, WHO/VDT/132. 16.Sept.1954.

63. RUITER, M., The possible role of pleuro-pneumonia-like organisms (P.P.L.O.) as aetiological agents in non-gonococcal urethritis.
WHO/VDT/127. 10.Sept. 1954.

64. DIENES, L., and BERG, R.L., A statement on our recent observations on the pathogenicity of pleuropneumonia-like organisms in the human genito-urinary tract.
WHO/VDT/121, 15.July, 1954.

65. SOREL,CL., Remarks on the pleuropneumonia-like organisms and the L-form of bacteria in

venereology.
WHO/VDT/123. 21. July. 1954.

66. STOKES JOAN,E., Human infection with pleuropneumonia-like organisms. The Lancet .5.Feb.1955.

67. KLIENEBERGER-NOBEL, E., Micro-organisms of the P.P.group, their nature, pathogenicity and modes of infection in relation to their possible harmfulness in human genito-urinary diseases.
WHO/VDT/28. June 1954.

68. FREUNDT. E.A., Occurrence of Ecology of Mycoplasma Species (pleuropneumonia-like organisms) in the male urethra.
Brit.J.of Vener. Dis.Sept.1956.32.p.188-194.

69. JEAN BRISON., Non-gonococcal inclusion urethritis.
WHO/VDT/125. 28. July, 1954.

70. LEJMAN,K., Sur la présence de phénomènes du type L.E. et autres types d'inclusions dans les frottès Vaginaux de petres blanches et uréthraux dans les uréthrites non gonococciques chez l'home.
ACTA DERM-VENER,STOCKHOLM, No.2. Vol.35.1955.

71. SMITH,K.M., and LAUFER, M.A., Edited by., "Advances in Virus Research". London, Academic Books Ltd.1955.

72. DUREL,M.P., et al. Pseudo gonococcic à inclusion intrecellulaires. Importance biologique et clinique.
BULL. SOC.FRANC.D85. 57:121-123.1950.

73. RHODES, A.J., and van ROOYEN, C.E., Textbook of virology for students and practitioners of medicine.
London, 1953. Bailliere, Tindall,Cox.

74. WILLCOX,R.R., Attempts to prove or disprove a virus

aetiology of non-gonococcal urethritis.
WHO/VDT/126. 1.Sept. 1954.

75. DIENES, L.L. Organisms of Klieneberger and strepto-bacillus moniliformis.
J. Infect.Dis., 65:24-42. 1939.

76. DIENES, L.L. The isolation of L-type culture from Bacteroides with the aid of penicillin and their reversion into the usual bacilli.
J.Bact. 56.:445-456. 1948.

77. KLIENEBERGER-NOBEL, E. Origin development and significance of L-forms in bacterial cultures.
J.General Microbiology. 3: 434-443. 1949.

78. HARKNESS, A.H., and HENDERSON-BEGG, A.
The significance of P.P.L. or "L-organisms" in non-gonococcal urethritis, Reiter's Disease, and Abacterial Pyuria.
Brit. J. of Venereal.Dis., Vol.24. 1948.

79. DIENES, L.L. and EDSALL, G., Observation of the L-organisms of Klieneberger.
Proc.Soc.Exper.Biol.Med. 36:740.1937.

80. TULASNE, R., and MINCK, R., Relationship between the P.P.L.O. and L-forms of bacteria.
Bacteriological identification of the P.P.L.O. in the human genital tract and sources of error.
WHO/VDT/116.1. July 1954.

81. DICKSON WRIGHT, A., and WILCOX, R.R., Carcinomatous urethritis, Brit.Med.Journal. Feb.18.1956.p.384.

82. DUREL, P., SIBOULET, A., et al. non-gonococcal urethritis in males. WHO/VDT/126. 1st Sept., 1954.

83. MIDANA, A., and SERRI, F., The epidemiological position of non-gonococcal urethritis in Italy. Clinico - statistical considerations. WHO/VDT/133.17.Sept. 1954.

84. IKEJIANS, G., (1955) West African Med.J. V.4.(N.S.) 25-9 (Bull.Hyg. 1955. 760).

85. GARTMAN, E., and LEIBOVITZ, A., (1955) Brit.J.Vener. Dis. Vol. 31. 92-7 (Bull.Hyg. 1955. 970).

86. GRIMBLE, A., and CSONKA, G.W., (1955) Brit.J.Vener.Dis. v.31. 228-34 (Bull.Hyg. 1956. July).

87. MAYNE, G.O. (1955) Brit.J.Vener.Dis.v.31 98-105 (Bull.Hyg. 1955. 969).

88. GRANT, R.N.R., Non-specific urethritis. Brit.Med. Journal April. 28. 1956. p. 980-1.

89. STEFL, J., Aetiology of non-specific urethritis Brit.Med.Journal April 10, 1954. p. 877.

90. WILLCOX, R.R. Researches in aetiology of non-specific urethritis. Brit.Med.Journal. Jan.2. 1954. p.13-15.

91. FORD DENYS, K., Human tissue culture studies of non-gonococcal urethritis. Brit.J.of Venereal Dis., Sept. 1956. 32. p. 184-187.

92. LYDON, F.L., Non-specific urethritis. Brit. Med. Journal Feb. 27.1954. p. 519.

93. KEKWICK,A., Dangerous reactions to sulphonamides and antibiotics. Brit.Med. Journal, April 7, 1954, p.796-798.

94. ORPWOOD PRICE, I.N., Test for Venereal Diseases. Brit.Med.Journal,March 6, 1954.p.575-6.

95. BOURNE, G.H., Edited. Cytology and cell physiology. Oxford 1951.

96. SHACKMAN, R., and MESSENT, D., The effect of an indwelling catheter on the bacteriology of the male urethra and bladder. Brit. Med.Journal, Oct.1954. p.1009-1012.

97. FERGUSSON, J.D., and GIBSON, E.C., Prostatic smear diagnosis. Brit. Med. Journal. April.14.1956. p.822 - 825.

98. O'SHAUGHNESSY, E.J., PARINO, P.S., and WHITE, J.D., J. Amer. Med. Ass. 1956. 160. 540.

99. HARKNESS, A.H., and BUSHBY, S.R.M., Non-gonococcal urethritis with special reference to treatment. WHO/VDT/117. 9. July. 1954.

100. HARKNESS, A.H., The cutaneous manifestations of gonorrhoea. Brit. J. of Vener. Dis., 21.93. 1945.

101. MYRES, J.L., and BRADLEY, D.F., Primary pustular gonorrhoea of the skin (a sixth proved case of primary cutaneous infection of N.gon.) Arch. Derm. and Syph. Nov. 1953.

102. WILLCOX, R.R. Erythromycin in non-gonococcal urethritis. WHO/VDT/120. 14. July. 1954.

103. WILLCOX,R.R. Erythromycin and Tetracycline in the treatment of non-gonococcal urethritis. WHO/VDT/128. 15. Sept., 1954.

104. WILLCOX,R.R. A comparison of Terramycin and Aureomycin in the treatment of non-gonococcal urethritis. WHO/VDT/119. 14. July. 1954.

105. VALENTINE, F.C.O. and SHOOTER, R.A., Recent advances in chemotherapy. Vol. 3. Antibiotics 1954.

106. MESSENT, A., and SHACKMAN, R., Non-Tuberculous and Tuberculous Epididymitis. Brit. Med. Journal. March 12.1955.p. 643-645.

107. CHENG, K.K. The experimental production of bronchiectasis in rats. J.Path.Bact.1954. 67. 89-98.

108. MAXWELL FINLAND., Clinical uses of currently available antibiotics. Brit.Med.Journal. Nov.21.1954. p. 1115-1121.

109. COSTE, F., and BOUREL,M., Importance of Non-gonococcal urethritis in rheumatology. WHO/VDT/118. 12. July. 1954.

110. THYGESON PHILLIPS., Inclusion urethritis and cervicitis. WHO/VDT/129. 18. Sept., 1954.

111. BOSZJAN, G., O naturze wirusów i bakterii Warszawa 1950.

112. HARRISON, L.W. Non-venereal urethral discharge. "The Bulletin of the Institute of Technicians in Venereology". December 1956.

113. RÖCKL and NASEMAN., Die Pleuropneumonie ähnlichen organism (P.P.L.O.) und ihre Bedeutung für die unspezifishe urethritis. Zentralblatt.Bakter. Orig.1956-165-313.

114. KLIENEBERGER-NOBEL, E., Über die WESEN-VERSCHIEDENHEIT der peripneumonie - ähnlichen Organismen und der L-phase

der Bakterien. Zentralblatt.Bakter Orig., 1956. - 165. 329.

115. SHEPARD, M.C., T-form colonies of P.P.L.O. J. Bact. 1956. 71. 362.

116. MELEN and GOTTHARDSON. Complement fixation with human P.P.L.O. Acta Patholog. et Microbiol.Scand. 1955. - 37. 196.

117. EDWARD, D.Gff.The Pleuropneumonia group of organisms and their significance in genital infection. Brit. Journal Vener. Dis.,1952. 28. 89-96.

SUMMARY.

of the Thesis "URETHRITIS" submitted for the degree of Doctor of Philosophy of the University of Glasgow.

by

Tadeusz A.H. Pasieczny, M.D. (Warsaw).

Summary.

Material for this work was collected between 1950 and 1957. The thesis is divided into four parts.

A. "Balanitis".

This part contains cases of "Balanitis" in which urethritis was a prominent symptom. One hundred and ninety-eight cases were investigated. In only 13 cases was urethritis severe enough to warrant the diagnosis of "balano-urethritis". This part also contains all those cases described in the Appendix under the heading "Miscellaneae", complicated in varying degree by urethritis. Some cases were of venereal origin, several not. Several cases were actually dermatoses.

It has been clearly shown that only rarely do cases require special treatment and subsequent observations after clinical cure and test of cure. The 13 cases of "balano-urethritis" fall into this category. Treatment consists of one or more of the following:- irrigations; sulphonamides; antibiotics; urological, radiological or surgical interventions.

This part emphasizes one important point, namely that many cases of urethritis are secondary to a large group of diseases which may be venereal or non-venereal.
The diagnosis of non-specific urethritis of unknown origin would be made less frequently if a full investigation were made to exclude these diseases, which are often the primary cause of the urethritis.

B. "Gonorrhoea mixed with other organisms".

Thirty-seven cases were investigated between 1953 and 1957. The commonest combinations of mixed infections were Gonococci with:1) Diphtheroids, 2) Staphylococci and 3) Coliform bacteria. Combined chemotherapy (sulphonamide-

antibiotic) in mixed infections is described and the indications for this therapy and the prevention of acquired drug-resistance. In all cases of mixed gonorrhoea cultures and sensitivity tests are obligatory, because microscopical examination of smears is insufficient. The selection and administration of therapeutic agents should only be decided after culture and sensitivity tests have been performed. In mixed infections all the infecting organisms should be regarded as of equal importance. Treatment consists of penicillin together with any other appropriate antibiotic or sulphonamide. These cases require longer observation after final test of cure than simple Gonorrhoea. They should be periodically examined subsequently, especially, if there had been prostatic involvement.

C. "Bacterial Non-Gonococcal Urethritis" (B.N.G.U.).

One hundred and seven patients and 43 controls were investigated. The incidence of venereal B.N.G.U. in my experience is much higher than that of the non-bacterial venereal condition. It is approximately twice as frequent. This is the reverse of what other workers have found in other areas.

Each case must be carefully investigated to establish the correct diagnosis, which in many instances is much more difficult, than simple gonorrhoea. Examination of several smears, cultures, and sensitivity tests are obligatory. Before taking specimens, careful cleansing of the meatus is essential. Prostatic investigation is very important, and valuable especially in cases, with recurrent urethritis, and cases of previous gonococcal infection. In time B.N.G.U. treatment is indicated as a rule. Some cases may have to be treated before cultures are available (e.g. sailors).

In most cases treatment should be withheld until the results of cultures and sensitivity tests are to hand. The general principles of treatment, observation and tests of cure are as stringent as for gonorrhoea. Patients should be warned about the consequence of failure to observe these principles.

D. "Abacterial Urethritis" (A.U.).

No bacteria are found in the exudate either on direct examination or by culture. In my experience this is a relatively rare disease. Treatment is very difficult. Complications are much more frequent than in B.N.G.U. or in gonorrhoea. The chief complications are epididymitis and prostatitis. The latter usually recurs in a asymptomatic form. In addition recurrences are common in A.U. Therefore, this type of urethritis must be carefully and conscientiously investigated and thoroughly treated.

One hundred and three cases were investigated for Trichomonas Vaginalis, for inclusion bodies and for P.P.L.O. in some of which positive results were obtained. Also for bacteria in the "L" form of which there were 2 probable cases. Spirochaetes were found in no case.

Complement fixing antibodies were found in all cases where P.P.L.O. were isolated, the highest litre being 1:8.

P.P.L.O. appears to be saprophytic in humans. Under certain conditions it may acquire pathogenic features, which enable it to evoke serious inflammation and complications in the urethra. The importance of this is emphasized by the frequency of relapses, even without further sexual intercourse. It is more frequent in females than in males. In male urethritis it is contracted by sexual intercourse. The chronicity, complications and tendency to relapse of

this infection indicate, that treatment of this form of urethritis is essential, not only for medical but on social grounds.

Treatment consists of terramycin, aureomycin or chloramphenicol in that order of efficacy. Urethroscopy with the modified Swift-Joly instrument was used in some cases.