A STUDY OF EARLY SYPHILIS, ITS TREATMENT AND THE MANAGEMENT OF THE REACTIONS TO TREATMENT.

A THESIS

FOR THE DEGREE

OF

DOCTOR OF MEDICINE

OF THE

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SUBMITTED BY

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CONTENTS.

A STUDY OF EARLY SYPHILIS, ITS TREATMENT AND THE MANAGEMENT OF THE REACTIONS TO TREATMENT.

INTRODUCTION.

Syphilis has been recognised for at least four centuries. During this time it has received much attention and study and its protean manifestations including the late effects in the central nervous system, have come to be recognised.

Early accounts of the disease reveal its epidemic occurrence and malignant nature. The great syphilologists of the 19th century including Ricord (1), Fournier (2) and Hutchinson (3) also mention manifestations of greater severity than those encountered in cases of syphilis seen during the last decade. It appears therefore that the virulence of the infection has become attenuated over the intervening years or that racial immunity to the infection has increased. For the purposes of comparison it is, therefore, of value to record the findings of a study of primary and secondary syphilis as encountered at the present day. Venereal disease is truly a camp-follower of war and the opportunities for a clinical study of syphilis in the British Army during the recent world war have been unique.

The policy adopted in the British Army laid down that all cases of venereal disease must be admitted to the appropriate section of a military hospital and retained there until non-infectious. Amongst other advantages, this policy provided ideal conditions for the detailed study of the early manifestations of syphilis.

As these patients are subject to military discipline,

their treatment and subsequent observation were more complete than would have been possible in civilian practice. It was considered that a study and permanent record of such cases, infected in the United Kingdom, would be of value and that useful guides to treatment could be obtained by studying the results of the serological reaction of the blood in relation to treatment with various schedules of trivalent arsenical compounds and with penicillin. Furthermore, because patients who had severe reactions to treatment could be admitted to hospital I enjoyed unusual opportunities for the study of such complications and of investigating new methods of their treatment.

The resulting study falls into three sections:-

Section 1.

A detailed clinical study and analysis of the signs and symptoms of 250 cases of primary and secondary syphilis.

Section 2.

A study of the reversal of the serological reaction of the blood in relation to treatment with various treatment schedules.

Section 3.

A study of major reactions to trivalent arsenical compounds with special reference to new methods adopted in their management.

A DESCRIPTION OF THE PRESENT STUDY.

MATERIAL.

The clinical material considered in the first section of this study was confined to British personnel in His Majesty's Forces infected in the United Kingdom. All cases were admitted to wards under my care for a minimum period of twelve days, the average being nineteen days.

The case reports, diagnosis and treatment were carried out personally, as were all laboratory procedures with the exception of the serological reactions.

250 cases of primary and secondary syphilis were studied and a complete analysis is presented in Section 1.

The material considered in Section II is composed of the records of 979 patients. It was confined to patients treated in my wards and out-patient department over a period of two years in the United Kingdom and six months in the Central Mediterranean Forces.

All the material relating to treatment with the trivalent arsenical compounds was taken from the records of my out-patient department in the United Kingdom where the number of injections of the arsenical compounds was 8,000 per year. The study consists of 819 cases. The material relating to treatment with penicillin was studied in my out-patient department in the Central Mediterranean Forces and relates to 160 cases.

The cases considered in Section III were studied in my wards and out-patient department in the United Kingdom.

METHODS USED IN CASE TAKING, EXAMINATION AND LABORATORY PROCEDURES.

For the purposes of the first section of this study a special case record was prepared, the form of which was as follows

EARLY SYPHILIS.

Case No.

Name. No. Rank. Unit.

Age. Service. Date of Admission. Married/Single.

Concomitant diseases.

General Examination.

Cardio-vascular system

Respiratory system

Genito-urinary system

Alimentary system

Nervous system

Date of infection. Date when first lesion noticed.

Lesion first noticed. Local treatment.

Circumcised/uncircumcised.

Is the chancre typical. Yes/No

Chancre:
(1) Number
(2) Size
(3) Shape
(4) Position
(5) Base
(6) Edge
(7) Haemorrhagic line
(8) Haemorrhagic band
(9) Oedema
(10) Induration
(11) Discomfort
(12) History of trauma

Date enlarged glands first noticed.

Glands:	Inguinal.		Axillary.		Cervical.		Epitrochlear.	
	R.	L.	R.	L.	R.	L.	R.	L.
No.								
Size.								
Shape.								
Consistence.								

Date rash first noticed.

Description of rash and distribution.

Date mucous lesions noticed.

Description of lesions and distribution.

Symptoms of secondary syphilis.

Date of dark-ground examination of serum. Lesion. Result.

Date of gland puncture if performed. Group of glands. Result.

Details of Jarish-Herxheimer reaction.

Other reactions to treatment.

On admission to hospital the patient was examined stripped in a well lit theatre and the clinical details recorded on the case-sheet. The clinical examination was followed by dark-field examination of serum from a primary or secondary lesion, or if neither of these were available, by gland puncture in suitable cases. Following this, 10cc. of venous blood were taken for serological examination.

The patient was then interviewed privately and the nature of his infection explained to him. The history was then taken

It was found that by discussing the patient's problems sympathetically with him and gaining his confidence, a more accurate and detailed history could be obtained, justifying the time expended.

The exact date of the first appearance of some lesions could not be accurately obtained in some cases in relation to the time of infection and, in other cases, repeated exposures to infection obscured the date of infection. Many cases, therefore, had to be excluded from the statistical analysis in this study.

Dark-field Examination of Serum from Primary and Secondary Lesions

The technique used in dark-field examination of serum was as follows:-

(a) The patient was informed that the procedure was not without pain but was a necessary one and he was urged not to move.

(b) The lesion was thoroughly cleaned and rubbed with gauze soaked in normal saline.

(c) A piece of cotton-wool damped with surgical spirit was applied to the lesion for five seconds.

(d) The lesion was then dried with cotton-wool and gently compressed.

(e) The exuding serum was picked up in a fine glass capillary tube from the edge of the lesion and transferred to the microscope slide by sealing the distal end of the tube in a Bunsen flame and forcing the serum out on to the slide.

(f) A cover-slip was applied over the serum and a minimum of fifteen minutes was spent in searching the slide for Treponema

pallidum. If no T. pallida were seen the lesion was dressed with gauze soaked in normal saline and the procedure repeated on two successive days.

Gland-punctures.

In gland-punctures the "wet" method was used. 0.1cc. of sterile normal saline was injected into the gland from a 1.0cc. syringe, the needle rotated, the gland kneeded and the aspirated fluid examined. The result of the dark-field examination was recorded as one, two, three or four plusses.

++++ represented an average of more than two T. pallida per field.

+++ represented an average of one T. pallidum per field.

++ represented one T. pallidum to less than twenty fields.

+ represented less than one T. pallidum to every twenty fields.

Serological Reactions.

The serological reactions were confined to Wassermann and Kahn tests. The tests were not carried out personally, but were carried out at the same laboratory except for the Kahn tests recorded after treatment with penicillin. Wassermann Reactions were carried out according to the Medical Research Council Method I.(14). In the Kahn Tests the method was one using two tubes containing antigen-serum mixtures of 1 in 12 and 1 in 6.

Other Laboratory Procedures.

Blood counts were carried out personally, as were

estimations of serum bilirubin. The method of determining the serum bilirubin was a colorimetric one using Gibson and Goodrichs' modification of Van den Berg's method. (56) From considerations of space and for the sake of brevity, the case records which have been included in the third section are presented briefly. Negative findings unless considered important have not been included.

Photography.

Thephotographs included in Section I are taken from the material analysed and have been included to give completeness to the description and analysis of the cases.

SECTION I.

SECTION I.

A CLINICAL STUDY AND ANALYSIS OF THE SIGNS AND SYMPTOMS OF PRIMARY AND SECONDARY SYPHILIS IN A SERIES OF 250 CASES.

PRIMARY SYPHILIS.

Dark-field examination of serum from open lesions usually provides rapid and accurate diagnosis of primary syphilis; clinical criteria alone can never be considered adequate. The patient with the atypical primary lesion is no longer kept in suspense until the secondary stage of the disease develops. A certain diagnosis can be made and treatment started within hours of the first appearance of the chancre.

It is considered that the so-called "typical" chancre is not as common in present day practice as one is led to believe by many text books.

During the present study pyogenic infections including infections with the bacillus of Ducrey, have been seen which aped the Hunterian chancre and have been proved to be non-syphilitic by repeatedly negative dark-field examinations and serological reactions.

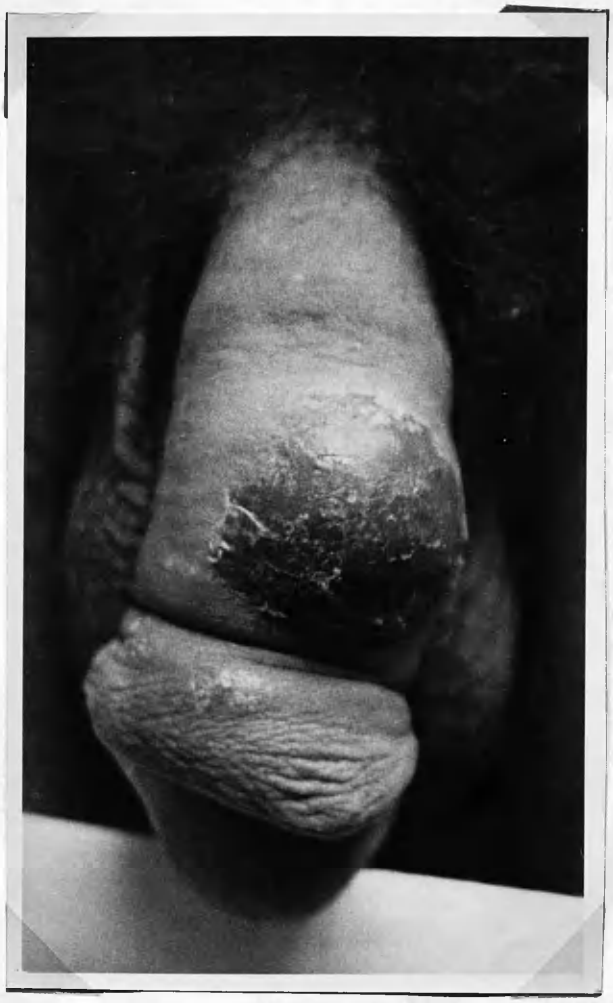
In 1939 and 1940 Unit Medical Officer's "index of suspicion" with regard to syphilis was extremely low due to the rarity of early syphilitic infections in peace time. As the snow-ball of venereal disease in this country gained size and momentum and as Medical Officers were required to give health lectures and examine troops for venereal disease the "index of suspicion" rose rapidly.

Among admissions to hospital in this series of 250 cases of syphilis were 67 non-syphilitic cases sent up with a tentative diagnosis of primary syphilis. This amounted to 27% of the total. Excluded from this number were cases of obvious scabies, usually with penile burrows. In these cases one dark-field examination of serum was carried out, blood was taken for a Kahn test and the patient was returned to his unit on the same day with instructions to report monthly for the next three months for a Kahn test.

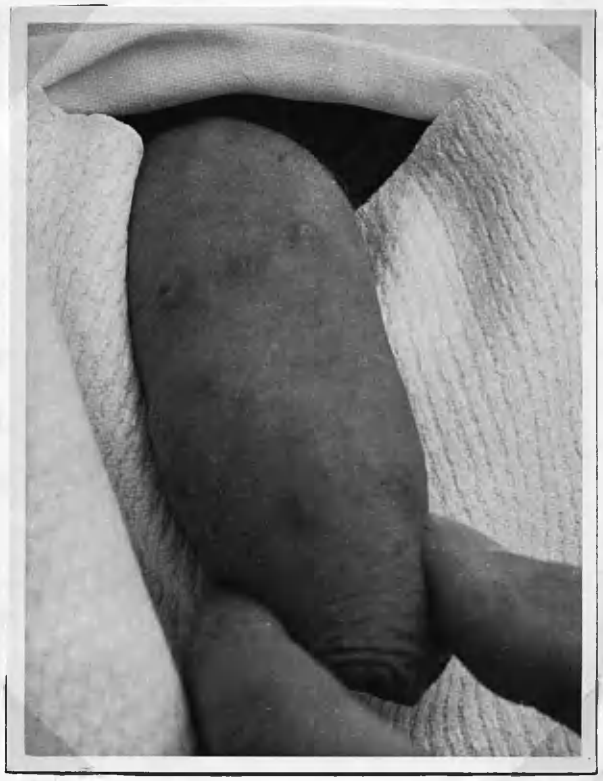
The diagnosis in the 67 cases was as follows:-

Chancroid	15
Erosive balanitis ...	12
Pyogenic infections (probably post-traumatic)	12
Infected scabetic lesions	10
Traumatic lesions ...	7
Herpes genitalis ...	6
Infected Tyson's gland ...	1
Epithelioma	1
Ulcers after removal of Condylomata acuminata...	1
Infected sebaceous cyst...	1
Cutaneous diphtheria ...	1

It is considered that this 27% indicates a fairly high "index of suspicion".



Post-scabetic abscess of the penis.



Scabetic burrows in the skin of the penis.

Chancroid simulating a primary chancre.

In all cases of primary syphilis before any laboratory diagnosis was attempted a note was made as to whether the chancre was typical or atypical. In this series only 64% of the cases were considered to be typical text-book chancres. This figure reflects the fact that many of the primary lesions were seen at an early age and had not developed induration or oedema, but also points to the great fallability of relying solely on clinical criteria for the diagnosis.

Incubation Period.

In 210 cases it was possible to determine the exact incubation periods. The average incubation period was 28.4 days. The shortest incubation period, occurring in two cases, was ten days and one case had the exceptional incubation period of 92 days. A tabulated comparison from various authorities is given below.

	Average Incubation	Shortest	Longest
Lees (6)	15-21 days	10 days	70 days
Burke (7)	30 days	10 days	84 days
Kampmeier (8)	10-20 days	8-10 days	90 days
Marshall (9)	25-28 days	10 days	70 days
Harrison (10)	28 days	-	-
Present series	28.4 days	10 days	92 days

The Site of the Chancre.

Primary chancres occurred in order of frequency on the following sites.

Mucous membrane of prepuce	...		24%
Coronal sulcus of glans penis	...		17%
Glans penis	...	...	12%
Frenum	...	...	11%
Shaft of penis	...	...	11%
Edge of prepuce	...	...	9%
Para-frenal	...	...	6%
Skin of prepuce	...	...	4%
Urinary meatus	...	...	2%
Extra-genital	...	...	2%
Scrotum	...	...	1%
Pubic area	...	...	1%

Characteristics of the Primary Chancre.

The typical or Hunterian chancre is usually described as a solitary, painless, round or oval ulcer with a depressed eroded surface of a raw ham colour. It has a raised edge with a thin haemorrhagic line and a firm "button like" indurated base.

The various characteristics found in my cases have been analysed.

Number.

Although most text books state that chancres are usually single, 45.4% of cases had multiple chancres. It was thought that multiple chancres might occur more frequently in the uncircumcised. As seen from the following statistics the difference is less than 1%. This negligible difference is accounted for by the "kissing" type of chancre in the uncircumcised.

Chancres in the circumcised:

Single	55%
Multiple	45%

Chancres in the uncircumcised:

Single	54.2%
Multiple	45.8%

A factor which may be responsible for multiple chancres rather than solitary ones is the presence of mucous lesions in the consort as it has been shown by Morgan (57) that inoculations with one to six spirochaetes in the rabbit do not cause infection It can reasonably be deduced that more positive inoculations will take place when the consort has mucous lesions.

All the extra-genital chancres in this group were confined to the lips, one being on the upper lip and the remainder on the lower lip.

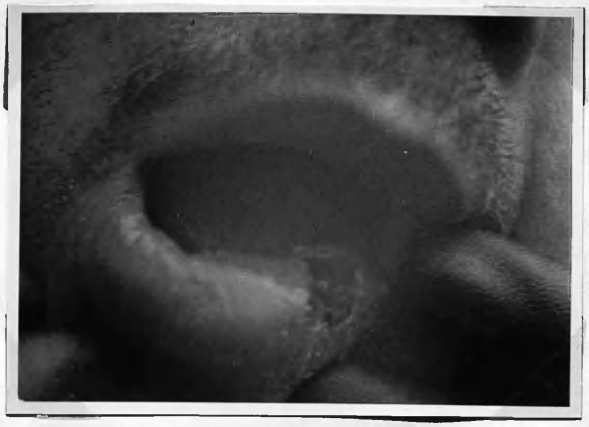
Size and Shape.

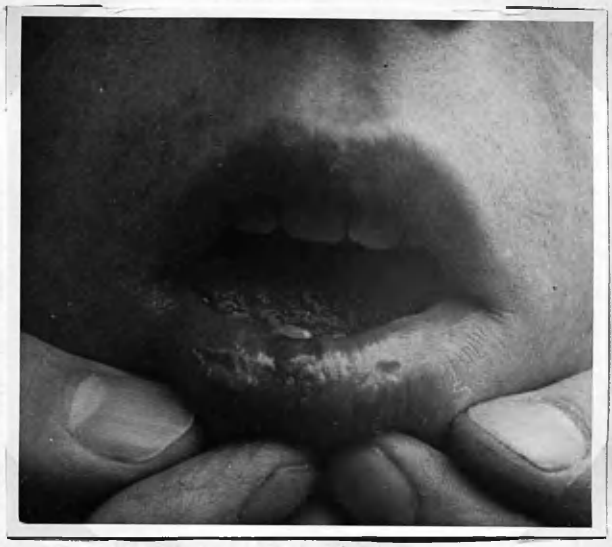
The chancres varied in size from that of a pin-head to one covering half the side of the shaft of the penis and measuring $3\frac{1}{2}$ inches by $1\frac{1}{4}$ inches. The average size was about $\frac{1}{2}$ inch by $\frac{1}{2}$ inch.

74% of the chancres were approximately round and the remainde were roughly oval in shape.

Pain and Discomfort due to the Chancre.

8.2% of the cases complained of pain and 62% complained only of discomfort. The usual complaint was one of slight discomfort often associated with rubbing of the sore against under-clothes





Extra-genital chancres of the lips.

or battle-dress trousers. Four cases complained of definite pain and in all these cases there was another, more obvious reason than the specific infection for this symptom. Two cases had phagedenic chancres, the third was a mixed infection of chancroid and syphilis and the fourth was a very large chancre of the shaft of the penis with marked secondary infection

The Base of the Chancre.

Unfortunately, in this series of cases, no chancre was seen at an early enough stage to be described as a raised papule with a smooth surface. All the lesions studied had some erosion of the surface. In 41% the base could be described as the colour of raw ham but in the remainder the base was a greyish-yellow colour with gross secondary infection.

The Level of the Base of the Chancre.

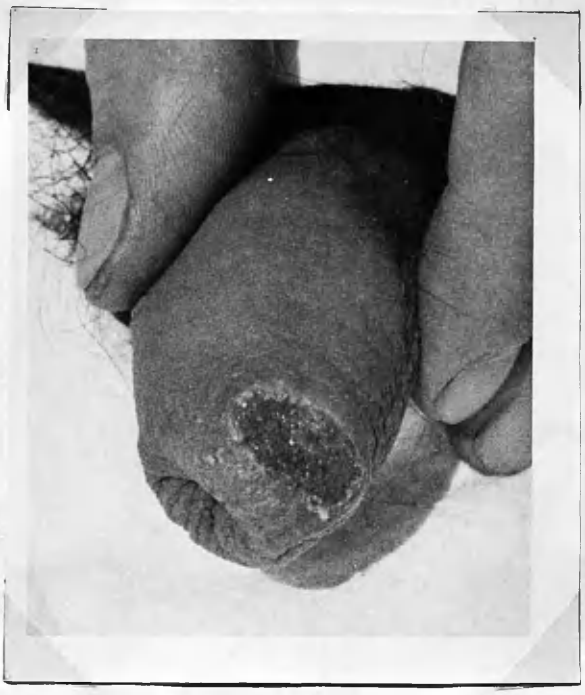
No real edge could be noted in 5% of the chancres, the base being on the same level as the surrounding integument. These cases were all seen within the first few days of the appearance of the chancre. In no case was the base elevated above the surrounding skin or mucous membrane.

The Edge of the Chancre.

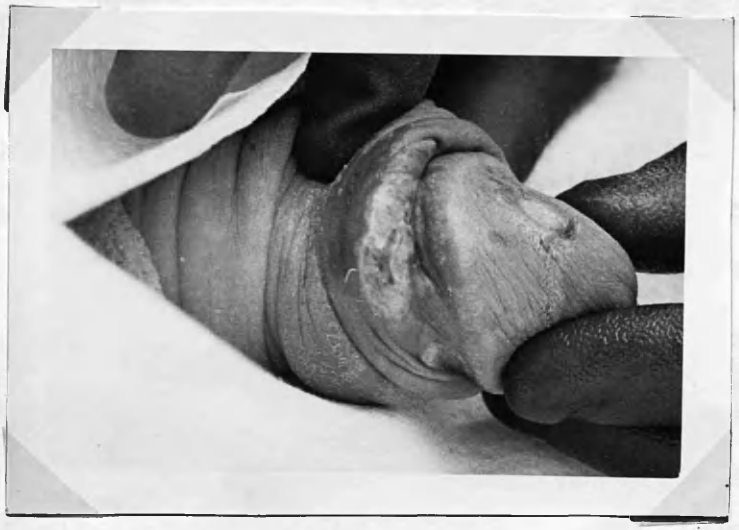
The edge of the chancre has been described by various writers as "Flat, not elevated or rolled" (5), "Slopes gently" (10) "Sharp regular edge" (9), "Raised" (6), "Border smooth with no undermining" (7) and "Even and rolled" (8). This diversity of description reflects on the diversity of appearance rather than on the acumen of the observers.

In the unhealed chancres observed, the edge could be

Primary chancre.



Primary chancre.



Multiple chancres.

described as rolled in 58%. punched out but not undermined in 21%, and shelving in 16% of cases. 5% had no clear cut edge, either elevated or depressed.

It is apparent that three factors:

(a) The age of the sore,

(b) The presence or absence of induration and oedema,

(c) The presence or absence of secondary infection,

are responsible for the type of edge seen in the primary chancre.

The Areola Surrounding the Chancre.

In 54% of cases a haemorrhagic line was noted running round the edge of the chancre. Only in 20% of cases did this line remain unbroken and surround the ulcer completely.

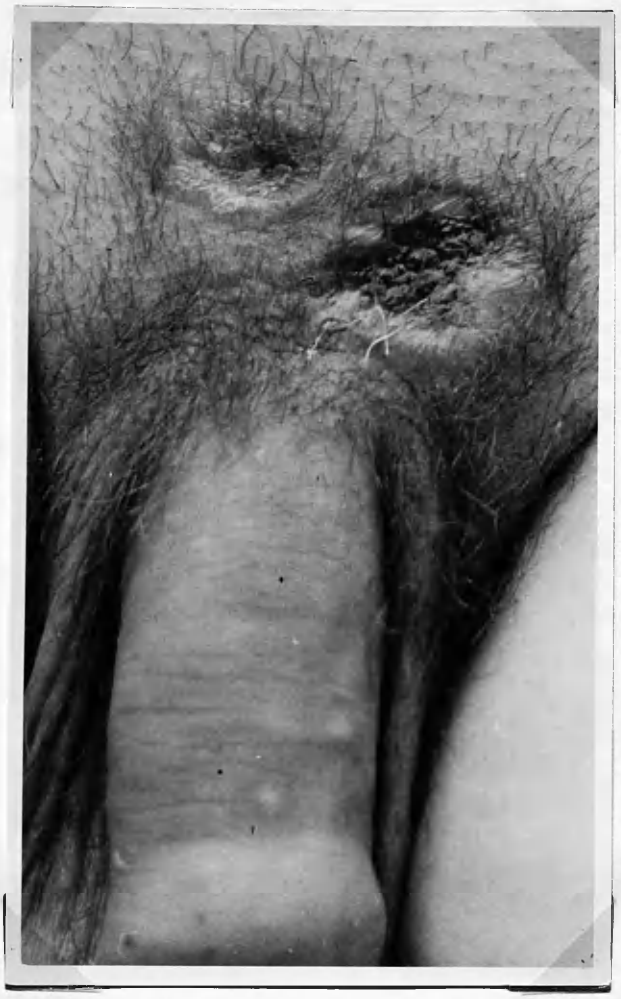
Harrison (10) states that in a chancre the areola is a band, while in chancroid it is a thin line. This could not be confirmed in this series of cases. Some cases could be described as a band and some as a line. Many exhibited both.

Induration and Oedema Around the Chancre.

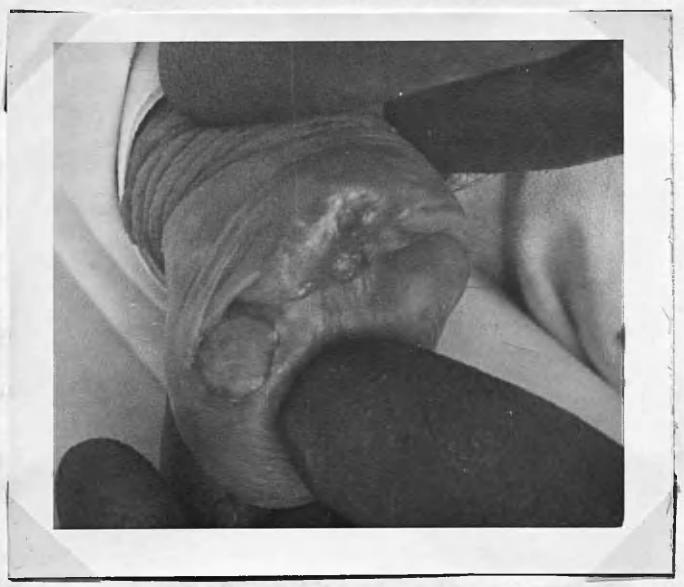
Induration and oedema were found to be present in 80% and 77% of the cases respectively.

It was noted that these signs tended to be minimal when the chancres were situated on the glans penis and that absence of induration occurred in the early chancres and absence of oedema in the early and late chancres.

The findings in primary chancres are summarised below.



Multiple chancres of the pubic area.



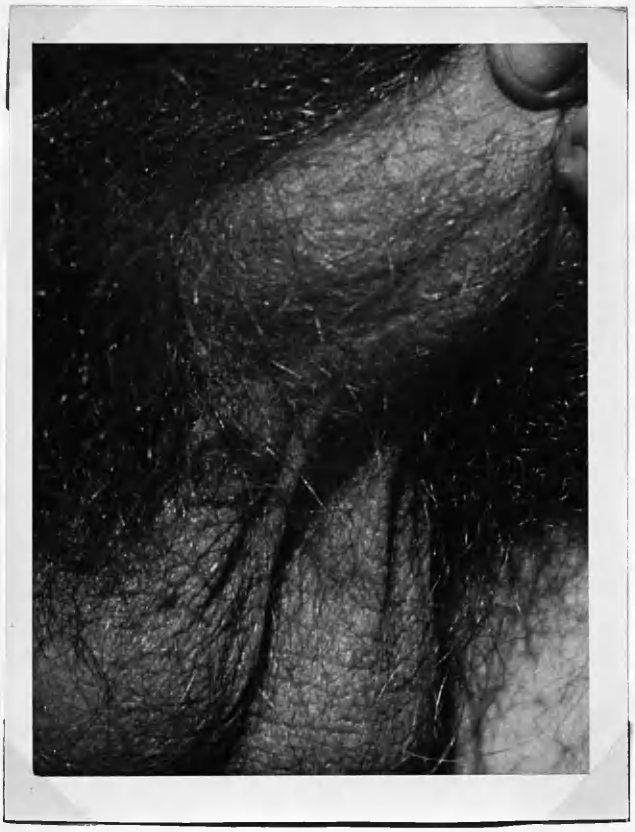
Multiple chancres on the glans and coronal sulcus.

Number,	Single	...	54.6%
	Multiple	...	45.4%
Size and Shape		...	$\frac{1}{2}$ in. by $\frac{1}{2}$ in.
	Round	...	74%
	Oval	...	26%
Pain	...	...	8.2%
Discomfort	...	...	62%
Surface.	Flat	...	5%
	Depressed	...	95%
Base,	Raw ham	...	41%
	Greyish-yellow		59%
Edge,	Rolled	...	58%
	Punched out..		21%
	Shelving	...	16%
	No edge	...	5%
Areola,	Present	...	54%
	Absent	...	46%
Induration,	Present	...	80%
	Absent	...	20%
Oedema,	Present	...	77%
	Absent	...	23%

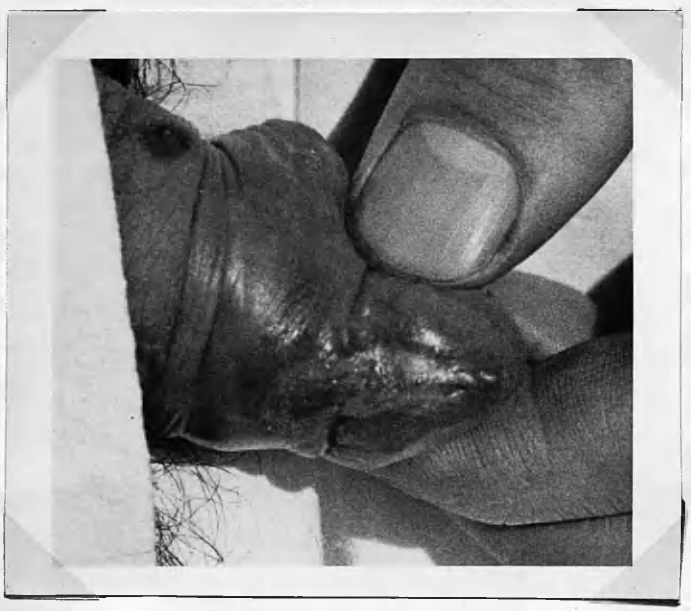
Adenitis Associated with the Chancre.

In a purely syphilitic genital chancre the associated inguinal adenitis has been described as "shotty" or "india rubber like".

It was observed that without secondary infection, glands smaller than a bean felt shotty and the glands had to be of



"French letter" chancre of scrotum.



Hour-glass chancre.

greater size than a bean before the typical india-rubber like consistency could be detected.

The occurrence of enlarged inguinal glands in relation to the date of infection was as follows:-

Week of infection.	Presence and size of glands.
1st week	Nil
2nd week	Nil or small (less than size of bean)
3rd week	small
4th week	Large. (greater than size of bean)
5th to 10th week	Large becoming generalised.

In twenty-four cases of genital chancre no enlargement of the inguinal glands was present. All these cases were seen before the fourth week of infection.

No case of bubo was encountered with a pure syphilitic infection and the india-rubber consistency of enlarged inguinal glands was usually present after the fifth week of infection. The site of the chancre did not always influence the side on which the inguinal glands first enlarged. A chancre on the right side of the penis might be accompanied by enlargement of the right inguinal glands alone, or the left inguinal glands or both.

Dark-field Examination of Serum from Chancres.

As already described, the results of the dark-field examination of serum from chancres was recorded by the following system.

++++ represented an average of more than two T. pallida per field.

+++ represented an average of one T. pallidum per field.

++ represented an average of one T. pallidum per 20 fields.

+ represented an average of less than one T. pallidum to every twenty fields.

These groups were further sub-divided according to the number of the dark-ground examinations carried out before a positive result was obtained. Serum from the chancres was examined on three successive days unless a positive result was obtained at the first or second examination.

The results were as follows:-

	++++	+++	++	+
Group I.				
1st Examination:	10	17	97	29
Group II.				
2nd Examination:	Nil	Nil	6	Nil
Group III.				
3rd Examination:	Nil	Nil	1	Nil

A positive result could not be obtained in 6% of cases. This constituted eleven cases.

5 cases: Chancres practically healed.

1 case: Chancre of lip with much secondary infection.

2 cases: Genital chancres having had local treatment. Gland punctures were positive.

3 cases: Genital chancres having had no local treatment. Gland punctures were positive in two of these cases.

It is considered that 94% of positive results in all cases is satisfactory and that in unhealed lesions a lower percentage of positive results is due to poor technique.

In this group of cases 28% had had some local treatment. While this did not materially affect the demonstration of

Treponema pallidum it was found that the results of examination from these cases fell into the ++ and + groups.

SEROLOGICAL REACTIONS IN RELATION TO:

(a) THE DURATION OF THE CHANCRE.

(b) THE DURATION OF INFECTION.

(a) Stokes (5) states that the Wassermann Reaction in cases where the chancre has been present for just over a week is positive in from 35% to 50% and climbs to 80% or more at the end of the 8th week. It is considered that this results from a relatively insensitive Wassermann Reaction. He gives the following table of methods and results.

Date of Appearance of Positive Serological Tests in Primary Syphilis.

Method	Per cent. Positive						Total Number of cases
	1 wk.	2 wks.	3 wks.	4 wks.	5 wks.	6 wks.	
Craig (W.R.)	36.3	59.3	69.9	77.2	81.3		600
Kolmer (W.R.)	44 - 75		82		94		
Irving (Kolmer) Stern (W.R.)	66.6	80					8
Willet Nagle (Kahn)	56.2	89.8	90.5	88.9	100		105
Klauder	36	64.7		70+	100		

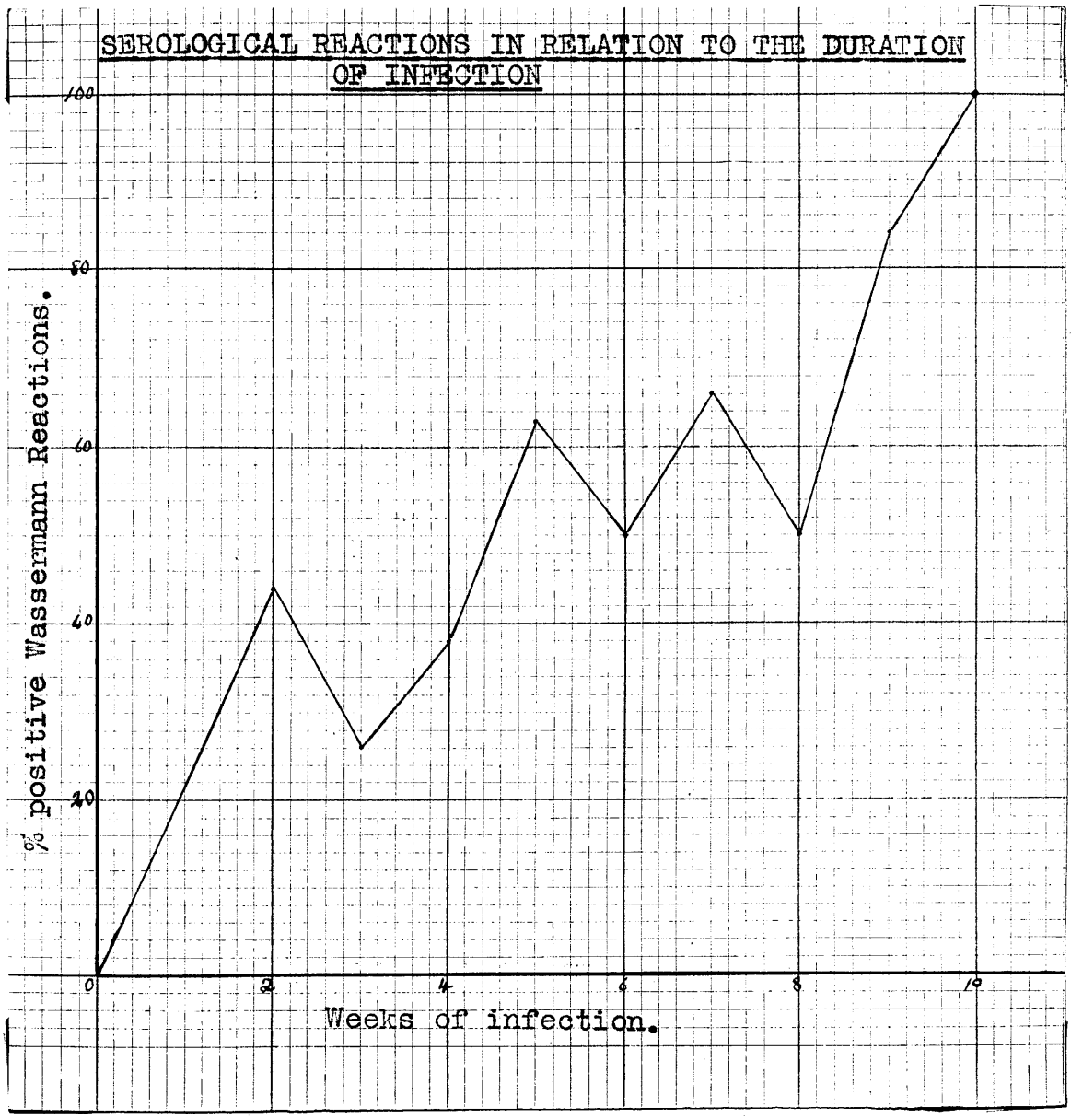
Burke (7) gives the following figures:-

Week of Chancre.	Percentage Positive Wassermann Reactions.
1	25
2	50
3	65
4	80
5	90

The Wassermann Reactions in the cases investigated were as follows:-

Week of Chancre.	Percentage Positive Wassermann Reactions.
2	40
3	44
4	59
5	100

(b) A graph showing the percentage of positive results in relation to the duration of infection is appended.


SEROLOGICAL REACTIONS IN RELATION TO THE DURATION OF INFECTION
% positive Wassermann Reactions.
100
80
60
40
20
0
2
4
6
8
10
Weeks of infection.

THE MANIFESTATIONS OF SECONDARY SYPHILIS.

Seventy five cases of secondary syphilis are included in this study and the manifestations are considered under the following headings:-

1. Cutaneous rashes.
2. Mucous lesions in the mouth.
3. Condylomata lata and moist papules.
4. Generalised Adenopathy.
5. Other manifestations of secondary syphilis.
6. The symptomatology of secondary syphilis.

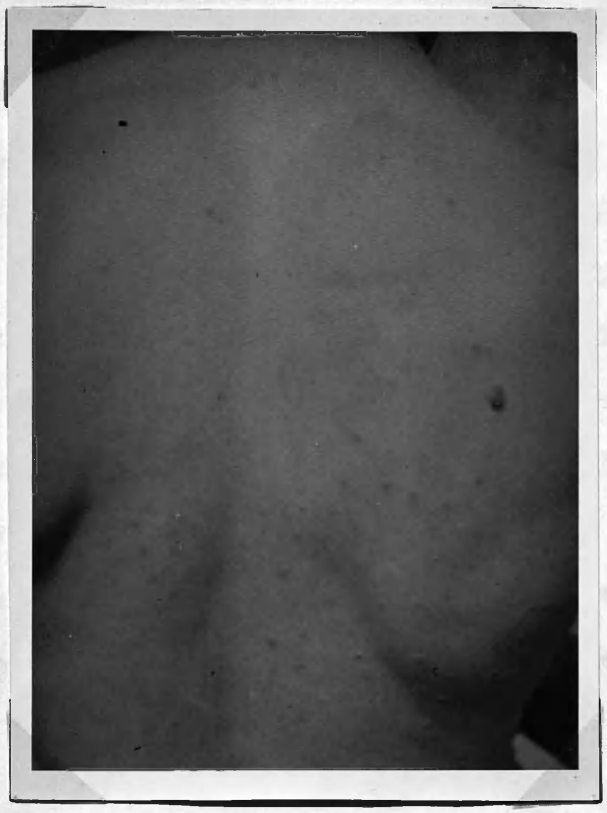
I. CUTANEOUS RASHES.

Cutaneous rashes due to syphilis were present in sixty three cases. In twenty one of these, more than one third of the total number, the rash was polymorphic.

The type of rash, the number occurring in this series and the average incubation period from the time of infection are tabulated below:-

Type of rash	No. of Cases.	Average incubation period in weeks.
Macular syphilide	44	11.2
Papular syphilide	33	15.0
Pustular syphilide	5	24.5
Ecthymatous syphilide	2	26.3

It is of interest to note that the pustular and ecthymatous syphilides occur much later in the infection than the macular



Maculo-papular syphilide.

Plantar Papular syphilide.

and papular syphilides.

The Macular Syphilide.

The average incubation period of macular syphilides calculating from the date of infection to the appearance of the rash was 11.2 weeks. As the average incubation period for all primary chancres in this series was 28.4 days the macular rashes appeared about 7 weeks after the primary lesion. This is in agreement with most authorities.

The distribution of this type of syphilide was found to be symmetrical and principally on the flexor surfaces of the arms, the sides of the neck, flanks, back and chest. The face, except for a few macules on the chin in five cases, was not affected and the lesions were usually scanty on the legs. The palms and soles were not affected.

The macules varied in size from about $\frac{1}{8}$th of an inch to half an inch and were round or oval in shape. The colour varied from a light to rose pink.

Nearly all the macular syphilides seen in this series exhibited a Jarish-Herxheimer reaction after the first intravenous injection of arsenic. No pigmentary syphilides of a macular type occurred in this group.

Papular Syphilides.

The papular syphilides have been divided up into the following sub-groups:-

Papulo-pustular syphilide.

Maculo-papular

Papular

Psoriasiform-papular

Follicular

Annular-papular

A comparative table of the frequency of occurrence and incubation periods has been compiled.

Type	No.	Incubation period in weeks.
Maculo-papular	19	14.5
Papular	7	15.2
Psoriasiform-papular	5	18.5
Follicular	1	Not known
Annular-papular	1	More than twenty weeks

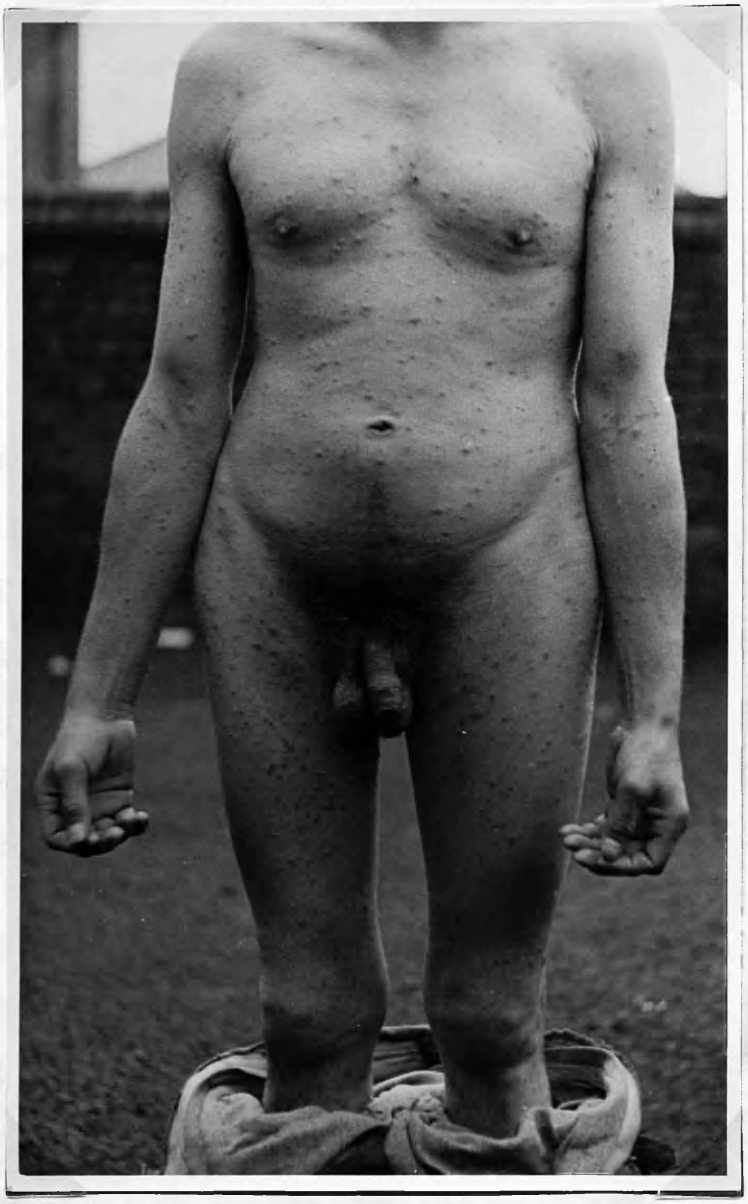
Maculo-papular Syphilides.

In cases where more than one type of rash co-existed the commonest combination was a macular and a papular rash.

The average incubation period of the maculo-papular rashes was three weeks longer than that of the pure macular rash, showing that while the papular types occur relatively early in the infection they are usually a later manifestation than the macular types.

In the maculo-papular type the distribution was similar to that of the macular syphilide except that the palms and soles were often involved, as was the face, especially at the hair line.

The papules were round and slightly elevated above the



Papulo-pustular syphilide.

surrounding epidermis. They were of a rose-pink colour and varied in size from $\frac{1}{8}$ to $\frac{3}{8}$ of an inch in diameter. In many cases the induration of the papules could be felt.

The Papular Syphilides.

Seven cases with a papular syphilide were observed. The average incubation period was 15.2 weeks.

This type of lesion was invariably found on the flexor surfaces of the limbs and trunk. In two cases the lower half of the face was affected and in one case the forehead. The palms of the hands were involved in one case and the soles of the feet in another.

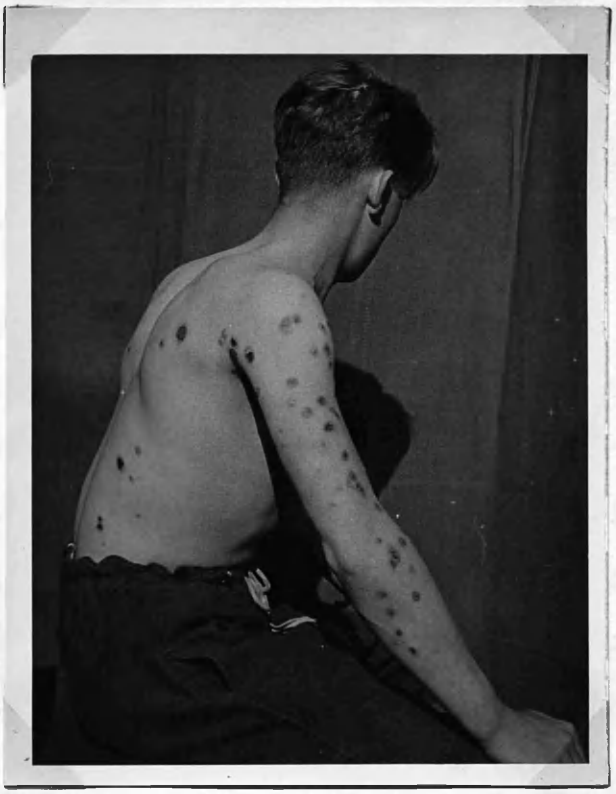
The papules varied in size from a pin-head to nearly half an inch in diameter. They were of a dusky pink to copper tint, flat topped and discrete. All the papules were indurated. One case was of the squamous type with scaling at the edge and some necrosis of the centres of the papules.

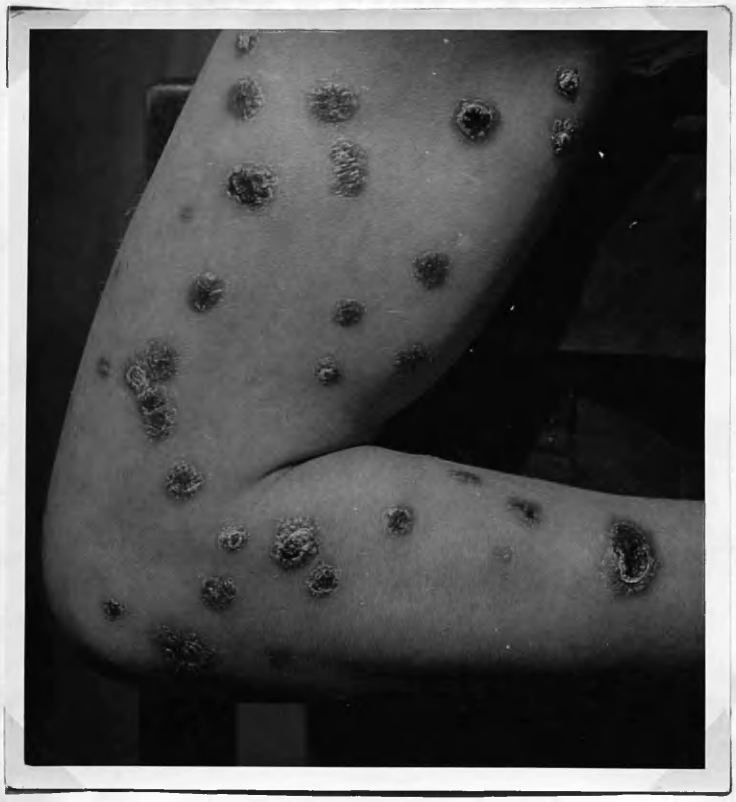
Psoriasiform-papular Syphilides.

Five cases of secondary syphilis exhibited papular rashes of the psoriasiform type and their average incubation period from the time of infection was 18.5 weeks.

In four of these cases, the distribution was the flexor surfaces of the limbs, the chest and the back. In the fifth case the palms and soles were also affected.

The psoriasiform lesions tended to be larger than any other type of papular syphilide. Some were more than one inch





Psoriasiform and Papulo-squamous syphilide with necrosis.

in diameter. The papules were of a distinct dusky copper hue, darker in colour than the pure papular rash. The scales were thin and easily removed. It was noted that in the psoriasiform-papular syphilides induration was marked.

Follicular Syphilides.

One case with a follicular rash was studied. In this case it was unfortunately impossible to obtain an accurate history as to the first appearance of the rash, the patient being rather dull mentally. The distribution was symmetrical and confined to the flexor surfaces of the arms, the chest and back. The scalp was not involved. The lesions were pin-head in size, brown in colour and conical in shape. The patient complained that the rash was accompanied by a slight itching.

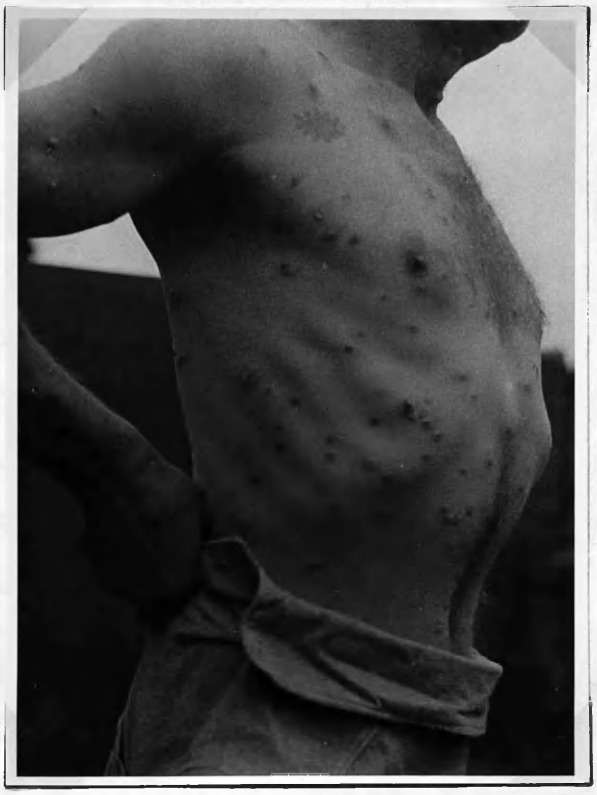
Annular Syphilides.

One case in this group had an annular syphilide. The incubation period could not be accurately ascertained but it was at least of twenty weeks duration.

The lesions occurred on the fore-arms and thighs, on the flexor surfaces and were both circular and polycyclic. The colour was a copper-red and the edges were raised. The centres were less intensely pigmented than the periphery and the lesions were indurated.

Pustular Syphilides.

Five cases of pustular syphilide were seen in this series. Only one was almost purely pustular, the remaining four being papulo-pustular. The average incubation period was 24.5 weeks.



Papulo-pustular syphilides.

The distribution of pustular syphilides was symmetrical and confined to the flexor surfaces of the limbs, the trunk and scalp. The face was least affected and the backs of the hands were not involved. In four of the five cases lesions were found in the scalp. In three cases the palms and soles were involved and in one case the palms only.

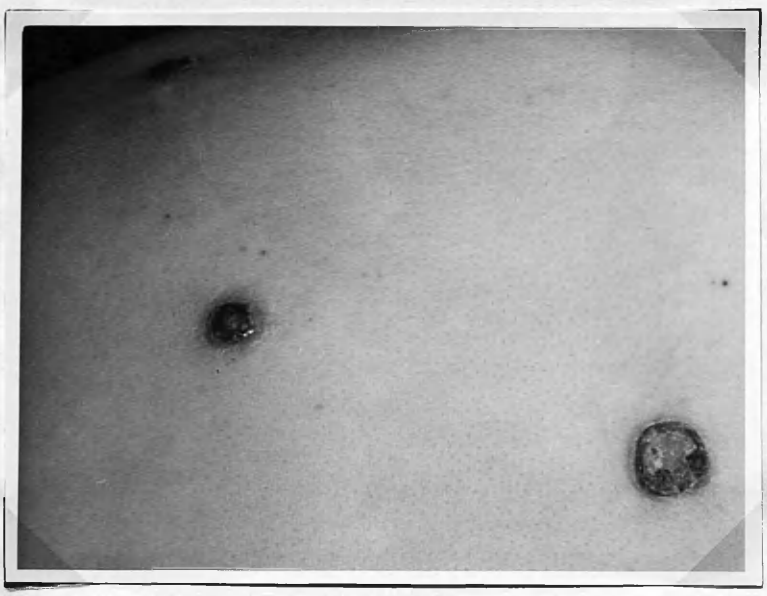
The individual lesions were discrete and dark red in colour with a crusted top. When the crust was removed a small ulcer was seen. The crusts varied in size from about $\frac{1}{8}$ to $\frac{3}{8}$ of an inch and there was very marked induration.

Ecthymatous Syphilides.

Two cases of rupial syphilides occurred in this series. The average incubation period was 26.3 weeks which is not in accord with Harrison's (10) statement that this type of eruption usually occurs about two years after the infection. The distribution in these cases was the scalp, face, upper arm, shoulders, back and chest.

The lesions were oval or circular in outline, discrete and indurated. They were covered with a conical, dark brown thick crust. After removal of the crust a punched out, indurated ulcer remained. The size varied from $\frac{1}{2}$ to $1\frac{1}{2}$ inches in diameter. After some weeks of treatment these lesions healed leaving a slightly depressed, thin, pigmented scar.

Papulo-ecthymatous syphilide.



Rupial syphilide.

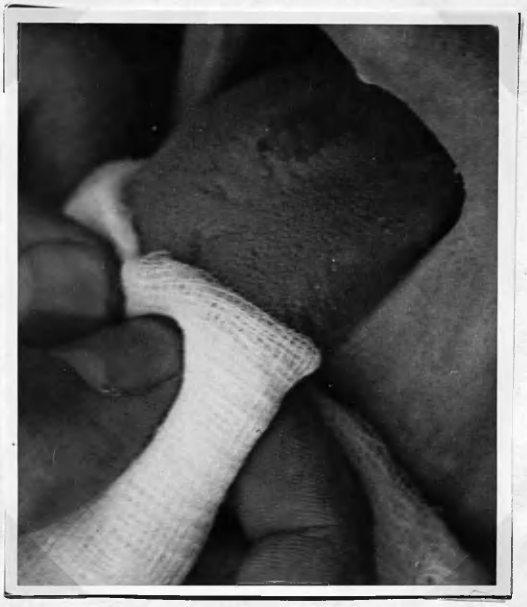
II. MUCOUS LESIONS IN THE MOUTH.

Mucous lesions in the mouth were studied in 44 patients. The distribution and frequency of occurrence of these lesions is shown in the following table:-

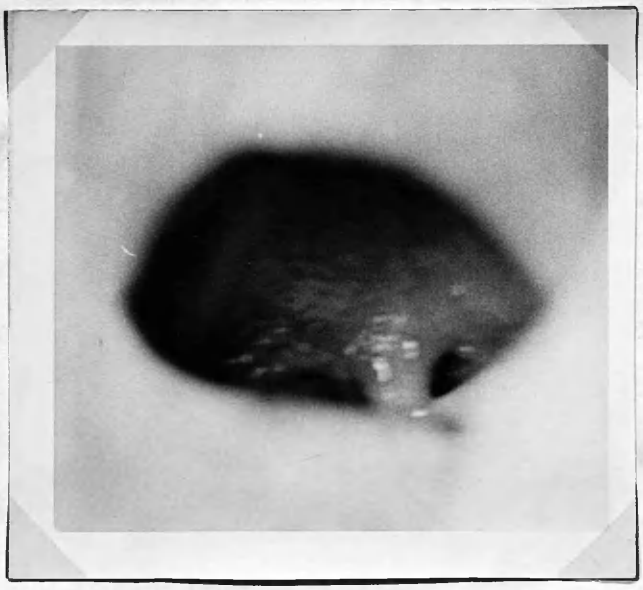
Distribution.	Frequency of Occurrence.
Tonsils	18 cases
Buccal mucosa	14 cases
Anterior pillar of the fauces	12 cases
Soft palate	3 cases
Tongue	3 cases
Floor of the mouth ...	2 cases
Uvula	1 case
Gums	1 case

The average incubation period of these mucous lesions was 12.2 weeks. They occurred most frequently on the tonsils as a milky-white patch with an irregular outline, or if the surface had been eroded, as a shiny granulating erosion. Occasionally ulceration was present with some destruction of tonsillar tissue and in these cases the base had a dirty sloughy appearance. When the tonsils were the site of a mucous lesion, it was not uncommon to find hyperaemia of the free border of the soft palate and of the uvula.

Lesions of the buccal mucosa were seen in fourteen patients. The lesions were round or oval in shape. If not eroded they appeared as silvery-grey plaques, slightly raised above



Eroded mucous patch on the tongue.



Mucous lesions of the soft palate.

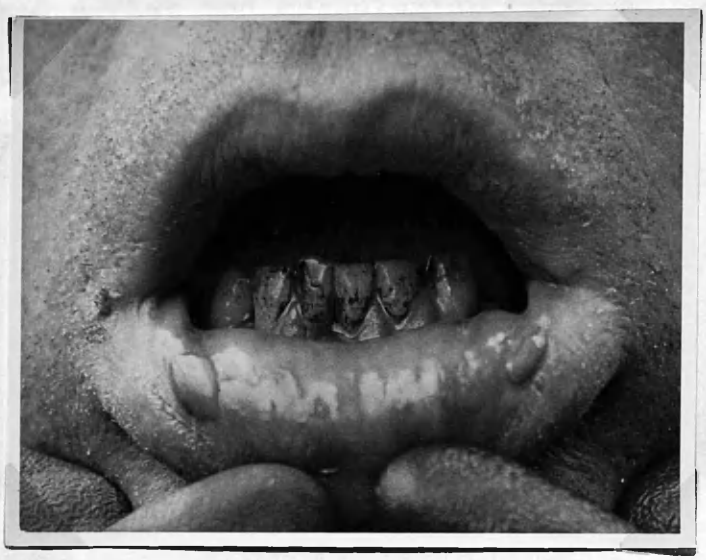
the surrounding mucosa and surrounded by a red areola. If the lesions were eroded they presented a flat, shiny, granulating surface, usually without so marked an areola. The lesions occasionally coalesced. No induration was present and the most common site was just posterior to the angles of the mouth at the level of the "bite" where the buccal mucosa is subject to the greatest amount of friction. The second commonest site was on the buccal surface of the lips, especially the lower lip.

Mucous lesions seen on the anterior pillar of the fauces were similar to those seen on the buccal mucous membrane unless ulceration was present. They were often associated with secondary lesions of the tonsils. When ulceration was present the base had a grey sloughy appearance and the edge a darker hue than the surrounding mucosa. The typical snail-track ulcer was present in four cases.

Mucous lesions of the soft palate and uvula were similar to those described on the buccal mucous membrane.

Three mucous lesions of the tongue were seen. All of these were more or less centrally placed. Two were situated at the junction of the anterior third and posterior two thirds of the tongue and the third lesion was situated more posteriorly. They appeared as a roughly circular, bald, red and atrophic patch. This appeared to be devoid of the normal papillae of the tongue. No hypertrophic lesions were seen on the tongue.

Lesions on the floor of the mouth occurred in two cases. They were situated anteriorly and were small oval red erosions which lacked the sheen of the surrounding mucous membrane. In

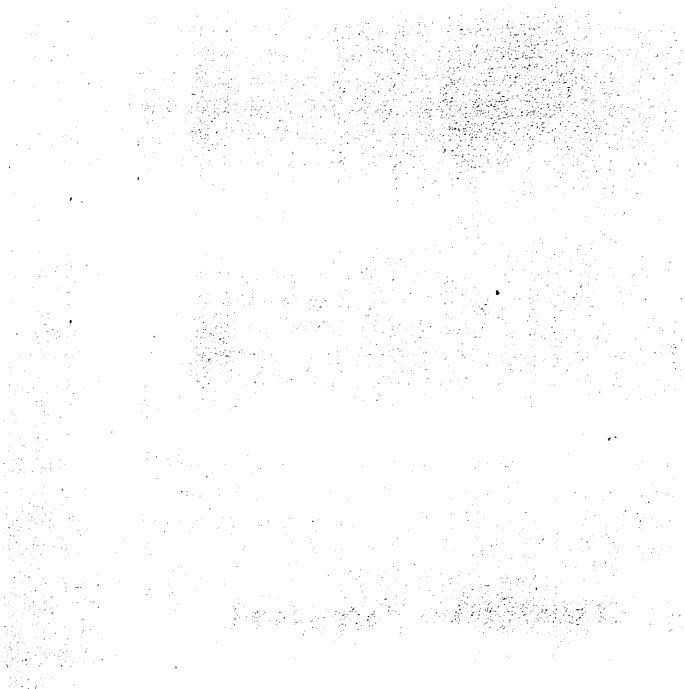


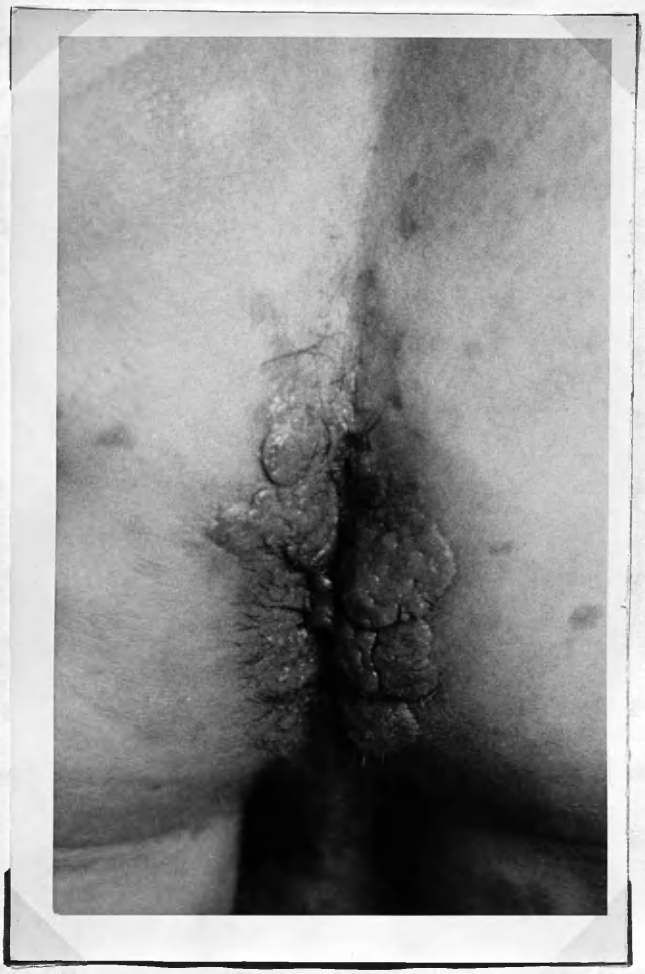
Mucous lesions of the lower lip.

one case an areola of a darker pink surrounded the erosion.

Mucous lesions were observed on the gums in one case. They appeared on the inter-dental papillae and spread round the dental margin of the gum. These lesions had the typical milky- white appearance but were not surrounded by a definite areola.

All mucous lesions of the mouth occurred, on an average, eight weeks after the appearance of the chancre and were characterised by a silvery-grey appearance, unless eroded, when they had a flat red granulating surface. No induration was present and with treatment all healed rapidly without pigmentation.





Peri-anal condylomata lata.

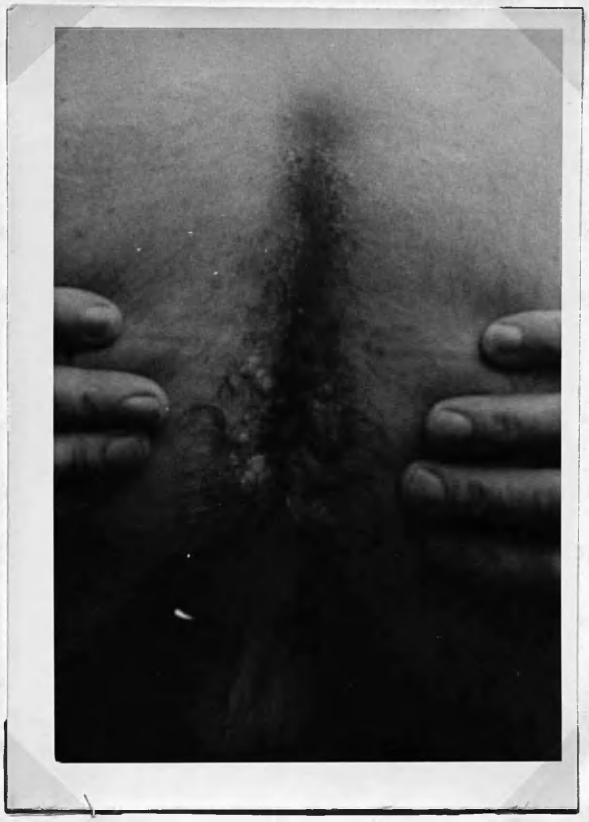
III. CONDYLOMATA LATA AND MOIST PAPULES.

Condylomata lata occurred in 23 cases. The distribution and frequency of occurrence are given below. The average incubation period was 22.3 weeks after the appearance of the chancre.

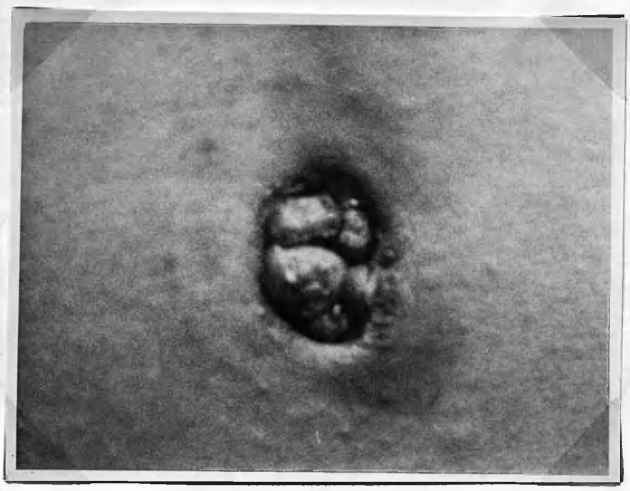
Distribution.	Frequency of Occurrence.
Peri-anal region and scrotum	16 cases
Scrotum	7 cases
Shaft of penis	2 cases
Thighs	2 cases
Umbilicus	2 cases
Axillae	2 cases
Between the toes	1 case

Condylomata lata were found most frequently in the peri-anal region and at the apposition of the buttocks. The colour varied from a silvery-pink to a dusky red colour and the lesions were flat topped and not pedunculated. Occasionally there was undermining of the edge due to the raised and hypertrophic nature of the lesions. The size varied from a few millimetres to ten centimetres when the lesions coalesced. The base was indurated and when condylomata were present in a patient with a low standard of personal hygiene they were covered with a purulent exudate and accompanied by a typical odour.

The muco-cutaneous junction at the anus and about $\frac{1}{4}$ inch of the surrounding skin was commonly devoid of condylomata lata.



Peri-anal condylomata lata.



Condylomata lata of Umbilicus.

Moist papules, however, were seen in this area.

Condylomata lata on the scrotum occurred most frequently on its posterior surface and could best be demonstrated by putting the scrotal skin "on the stretch". These lesions were smaller and less elevated than those found between the buttocks and were of a dusky red colour with occasional scaling of the top of the lesion.

When condylomata were observed on the shaft of the penis they were similar to the scrotal lesions. In one case, when seen on the thighs they were similar to the scrotal lesions but in the other case they were frambesiform and of a dusky blueish-red colour.

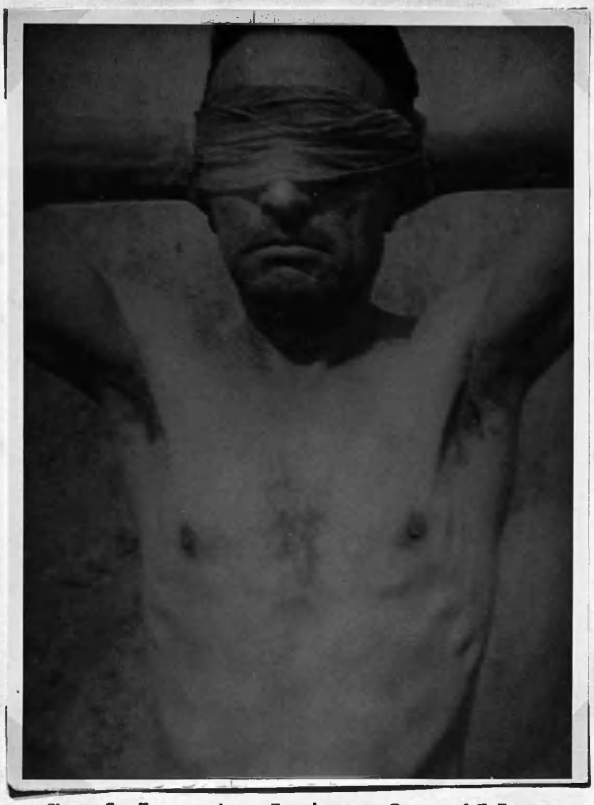
When observed in the axillae, umbilicus and between the toes they were greyish-pink in colour, elevated and flat topped.

Dark-ground examination of serum obtained from condylomata lata was invariably found to contain many T. pallida.

Moist papules were found with the following distribution and frequency:-

Distribution.	Frequency of Occurrence.
Scrotum	10 cases
Shaft of penis	8 cases
Glans penis and mucous ... membrane of prepuce ...	7 cases
Peri-anal region ...	7 cases
Thighs	1 case

The average incubation period of these lesions was 16.8



Condylomata lata of axillae.

Condylomata lata of scrotum.

weeks after the appearance of the chancre.

Moist papules most commonly appeared on the posterior aspects of the scrotum as pink shallow ulcers with a straight or shelving edge. Occasionally they were hypertrophic and had a base built up above the surrounding dermis. If much secondary infection was present the base became grey and sloughy in appearance.

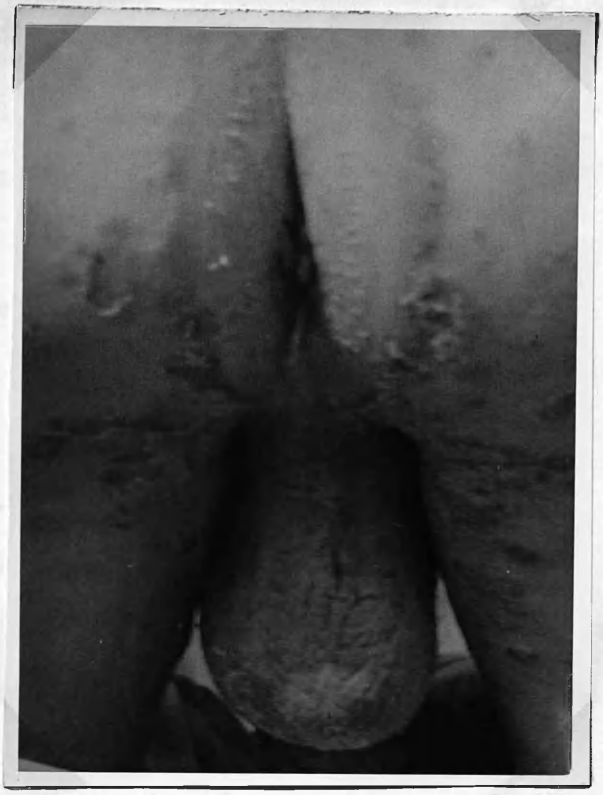
The average incubation period for these lesions was 16.8 weeks.

Moist papules on the shaft of the penis were seen most commonly on the ventral aspect of the proximal third and at the peno-scrotal angle where the penis and scrotum are normally in apposition. The lesions were oval or circular in outline and varied in size from $\frac{1}{4}$ inch to $1\frac{1}{2}$ inches in diameter.

The moist lesions seen on the glans penis, in the coronal sulcus and on the mucous membrane of the prepuce were pink in colour with a flat, eroded surface. Those seen around the anus varied in size from $\frac{1}{8}$ inch to $\frac{1}{4}$ inch and occurred in the folds of the mucosa. In two cases they were superimposed on external haemorrhoids. The papules were dark red in colour and had an eroded surface.

One case exhibited moist papules on the thighs which were similar to those observed on the scrotum. They were confined to the inner aspects of the upper thirds of the thighs.

Induration was present in all these lesions and the serum obtained from them contained many T. pallida.



Moist papules and condylomata lata.

Moist papules of penis and scrotum.

IV. GENERALISED ADENOPATHY.

The regional adenopathy in relation to the primary chancre has already been described.

On examination of a patient with secondary syphilis it was usual to find that even in the presence of a healed penile lesion the inguinal glands were larger than the other superficial lymph glands in the body. This was a universal finding when the penile lesion was unhealed.

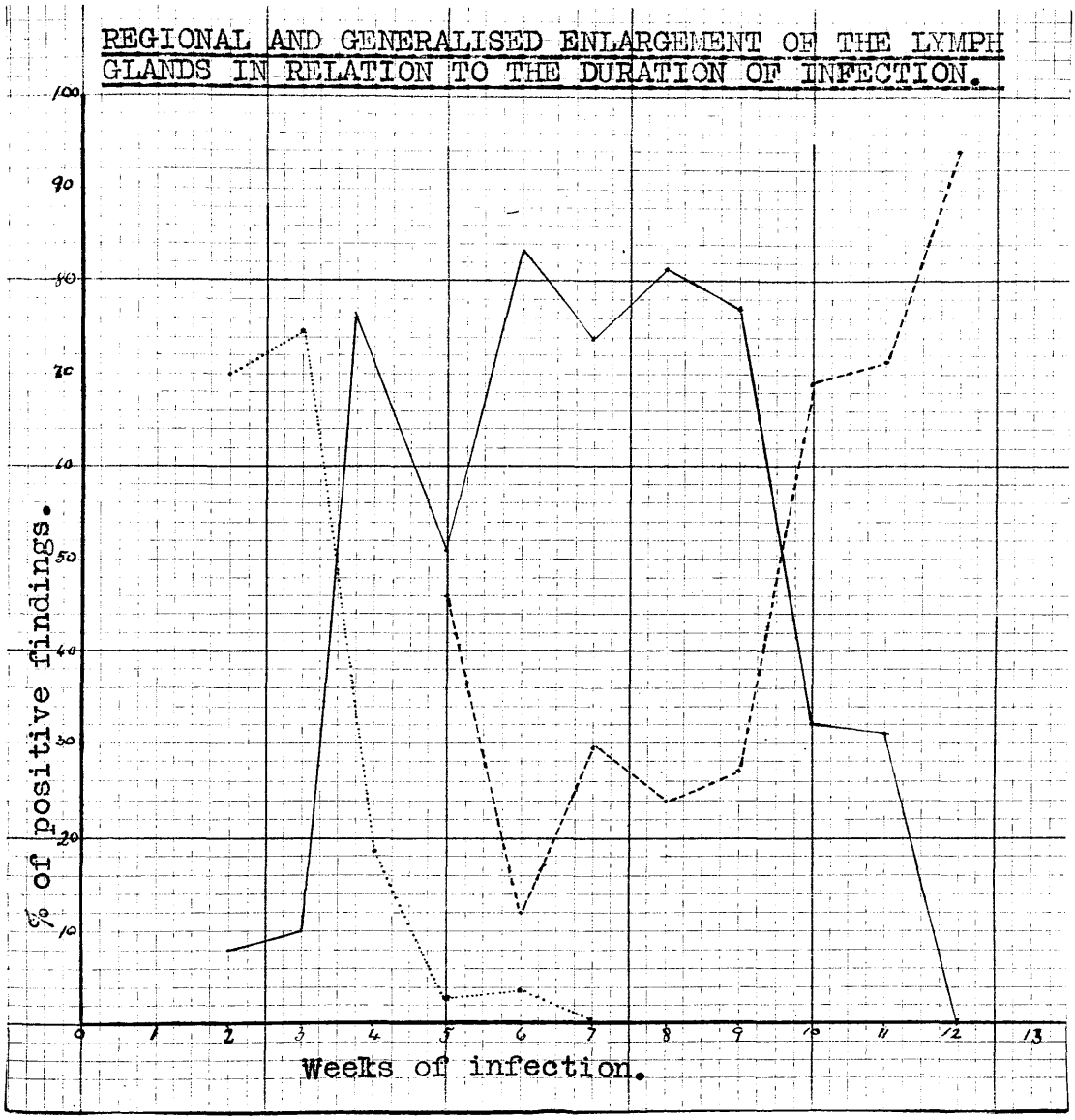
The superficial lymph glands in the neck, in both the anterior and posterior triangles, were commonly enlarged as were the glands in the femoral region. It was found more often than not that these glands had a shotty consistence rather than an india-rubber feel. This was directly related to the size of the glands which were about the size of a bean or less.

The epitrochlear glands were sometimes enlarged but as often as not only one was palpable. They were of the shotty variety and none enlarged sufficiently to have an india-rubber feel.

Most soldiers have palpable axillary glands whether they are suffering from syphilis or not. In a group of 200 cases suffering from diseases other than syphilis, 94% had palpable axillary glands varying in consistency from shotty to soft. It is considered that the frequent inoculations and vaccinations carried out in the army are responsible for this finding.

A graph is appended illustrating the change found in the superficial lymph glands of the body as the syphilitic infection progresses.

It is shown by the graph how the generalised enlargement of the lymphatic glands occurs about the 10th week of infection. In two cases where a generalised enlargement of the superficial lymph nodes was present but who presented no other clinical signs of secondary syphilis, a maculo-roseolar rash of a transient nature was seen after the first injection of neoarsphenamine.



..... Small inguinal glands.

———— Inguinal glands larger than a bean.

---------- Generalised enlargement of the superficial lymph glands.

V. OTHER MANIFESTATIONS OF SECONDARY SYPHILIS.

In four cases enlargement of the epididymis was present. This was unilateral in three cases and bilateral in one case. The incubation period varied from 12 to 32 weeks, the average incubation period from the date of infection being 24 weeks.

The epididymis was found to be enlarged and smooth and the swelling completely subsided after a few injections of neo-arsphenamine.

No enlargement of the liver or spleen attributable to syphilis was observed nor was there a case of syphilitic nephritis in this series.

One case of syphilitic iritis occurred in the 18th week of infection. The condition cleared up quickly with atropine eye drops and routine anti-syphilitic treatment.

VI. THE SYMPTOMATOLOGY OF SECONDARY SYPHILIS.

The symptomatology of 75 patients suffering from secondary syphilis is given below. Only 25 patients, one third of the total number, complained of any symptoms attributable to the syphilitic infection.

Sore throat (including Hoarseness)	15
Headache	9
Malaise	9
Loss of weight	6
Feverishness	4
Myalgia	2
Bone pains	1
Gastro-intestinal ...	Nil
Deafness	Nil
Insomnia	Nil

In no instance of primary syphilis could a definite history of constitutional symptoms be elicitated. A few patients with primary syphilis gave a history of headache in answer to a leading question. None complained of this symptom spontaneously and on further questioning the headaches bore no relation to the time of infection but had been occurring prior to infection. Stokes (5) quotes Fournier as estimating that 50% of women and 75% of men experience no constitutional symptoms from their infection but states that in his own experience 63% of women and 42% of men have constitutional symptoms. Burke's (7) figures agree with those of Stokes.

Sore Throat.

This was the commonest symptom encountered. Fourteen cases complained of a sore throat and ten had noticed a hoarseness in their voice.

In ten of the cases there were mucous lesions in the mouth as well as the laryngeal erythema.

Headache.

All types of headache have been grouped together. Of the nine patients complaining of headache eight complained of persistent diffuse headache and one of occipital headache. In six of the cases the headache was worse at night. No case with a localised headache and tenderness, suggesting a localised osteitis was encountered.

Malaise.

Nine patients complained of malaise, usually accompanied by some lassitude. In all cases, malaise was accompanied by other constitutional symptoms.

Loss of Weight.

Six patients gave a history of loss of weight, the amounts varying from three pounds to twenty pounds. This was a difficult sign to assess accurately as most soldiers have a very vague idea of their normal weight. As far as could be ascertained the average loss of weight in these cases was 6.2 lbs.

In one case the loss of weight was 20 lbs. The patient had florid secondary syphilis with mucous lesions, a rupial syphilide, sore throat, headache, malaise, feverishness and aching in the muscles of his limbs.

Feverishness.

Of the four patients complaining of feverishness all had temperatures above normal. The highest was 100.2 deg. F. and the average was 99.4 deg. F.

Myalgia.

Two patients complained of muscular pains. One complained of pains in the shoulder girdle and the other of pains in the muscles of all four limbs. Both cases reported that these pains were worse at night.

Bone Pains.

One patient in the 50th week of his infection complained of pain in his right tibia just below the tibial spine. There was a small area of tenderness at this point. The pain was worse after exercise. He did not give the typical history of nocturnal pain relieved by movement of the affected part. Radiological investigation revealed no bony abnormality.

CONCLUSIONS.

From the preceding study and analysis of this series of cases, the following conclusions can be reached:-

1. The average incubation period of primary syphilis is 28.4 days and the incubation period varies from 10 to 92 days.
2. The commonest site for a primary chancre is on the glans penis and prepuce.
3. The characteristics of a primary chancre vary greatly, the appearances being affected by the site and age of the chancre and by the presence or absence of secondary infection. Certain diagnosis cannot be made from clinical criteria alone.
4. The consistency of enlarged lymph glands due to a syphilitic infection depends on the size of the glands. The glands feel "shotty" if smaller than the size of a bean and have an "india-rubber" consistency if larger than a bean.
5. Diagnosis by examination of serum from unhealed primary chancres can be made in 94% of cases irrespective of whether or not the chancre has been subjected to local treatment.
6. The Wassermann Reaction of the blood is positive in 40% of cases after the chancre has been present for two weeks. This climbs to a 100% during the following three weeks.
7. Secondary syphilitic rashes occur in the following order and stage of infection:-

Macular rashes	...	11.2 weeks
Papular rashes	...	15.0 weeks
Pustular rashes	...	24.5 weeks
Ecthymatous rashes	...	26.3 weeks

8. Mucous lesions are seen most commonly on the tonsils and buccal mucosa and their average incubation period from the date of infection is 12.2 weeks.
9. Condylomata lata occur most frequently around the peri-anal region and scrotum and the average incubation period from th time of infection is 22.3 weeks. Moist papules are seen most frequently on the scrotum and the shaft of the penis and the average incubation period is 16.8 weeks.
10. Generalised enlargement of the lymphatic glands occurs about the tenth week of infection and the glands feel "shotty".
11. Only 33.3 per cent of cases suffering from secondary syphilis had constitutional symptoms.
12. No cases with proved bony lesions occurred in this series.
13. Syphilis as studied in this series of cases is a less virulent disease than that described by Hutchinson, Fournier and Ricord in the Nineteenth Century.

S E C T I O N II.

SECTION II.

A STUDY OF THE REVERSAL OF THE SEROLOGICAL REACTION OF THE BLOOD IN RELATION TO TREATMENT WITH VARIOUS SCHEDULES OF TRIVALENT ARSENICAL COMPOUNDS AND WITH PENICILLIN.

I N T R O D U C T I O N.

Unlike late syphilis, the treatment of the majority of cases of early syphilis permits and encourages standardisation. Treatment schedules with arsenic and bismuth usually follow one of two systems. In the continuous alternating system blocks of arsenical and bismuth injections alternate without rest periods until treatment is complete. With the concurrent intermittent system, arsenic and bismuth are given concurrently and a rest period is given between each block of injections.

In general the latter system is used in British practice and the continuous alternating system is advocated and adopted in America.

In the British Army the concurrent intermittent system is used. Treatment is divided into unit courses by rest periods of four weeks. In each unit course arsenic and bismuth are given on the same day, once a week, for ten weeks except for the first two injections of the first course. The initial injections are given while the patient is in hospital.

It was recommended that all sero-negative cases of primary syphilis should receive four courses of arsenic and bismuth, provided the serological tests remained negative throughout treatment. Other cases of "early" syphilis should receive three

full courses of arsenic and bismuth after the Wassermann Reaction has been found to be negative, serological tests being performed at the beginning of each course.(11). "Early" syphilis is diagnosed within the first four years of infection.

The arsenical preparations in routine use are various proprietary preparations of neoarsphenamine.

In the first unit course the initial dose is 0.45 g. and the subsequent nine weekly doses are 0.6g. In cases of secondary syphilis where certain vital structures, e.g. the larynx, are involved and in which a Herxheimer reaction might produce a fatal obstruction the initial dose is reduced or only bismuth is given, on the first day of treatment.

The bismuth preparations in routine use are either a suspension of bismuth metal in isotonic glucose or bismuth oxychloride suspended in a glucose solution. In this study the preparation used throughout was bismuth oxychloride, so that the effect of the bismuth injections would be constant.

During the 1914 - 1918 war it was found that a reduction in the amount of arsphenamine given in a unit course reduced the incidence of jaundice and dermatitis (12). In 1942 the routine in the Army was modified in an attempt to reduce the incidence of jaundice.

The courses given were as follows:-

Courses 1, 3 and 4.

Day.	Neoarsphenamine.	Bismuth.
1	0.45g.	0.2g.
5	0.6g.	0.2g.
12	0.6g.	0.3g.
19	Nil	0.2g.
26	0.6g.	0.3g.
33	Nil	0.2g.
40	0.6g.	0.3g.
47	Nil	0.2g.
54	0.6g.	0.3g.
61	0.6g.	0.3g.

Total arsenic = 4.05g.

Course 2 only.

1	Nil	0.2g.
5	Nil	0.2g.
12	0.6g.	0.3g.
19	0.6g.	0.2g.
26	0.6g.	0.3g.
33	0.6g.	0.2g.
40	Nil	0.3g.
47	0.6g.	0.2g.
54	0.6g.	0.3g.
61	0.6g.	0.3g.

Total arsenic = 4.2g.

It will be shown in Section III of this study that the reduction in the total amount of neoarsphenamine given in

these modified unit courses did not reduce the incidence of jaundice in the series of cases studied.

At the time when jaundice assumed epidemic proportions in the cases attending for anti-syphilitic treatment it was found that jaundice usually occurred during the rest period after the first course or about the beginning of the second course. The first two arsenical injections of the second course were therefore omitted to prevent adding further insult to a possibly already damaged liver.

Owing to the movements of military personnel from one station to another, it has been impossible to make any long term study of the results obtained from routine treatment schedules. A study of the results obtained from various unit courses has, however, been carried out by assessing the changes in the serological reaction of the blood thirteen weeks after treatment was started.

Prebble has described a unit course in which neoarsphenamine and bismuth are given bi-weekly (13). He has reported consistent reversal of the serological tests with this course. A series of cases was treated according to this schedule with the object of obtaining a yard-stick by which the results of other unit course studied, might be measured.

An analysis of six different schedules, covering a series of 829 cases of primary and secondary syphilis has been made.

All serological tests were Wassermann Reactions carried out at the same laboratory and using the Medical Research Council Method 1.(14). Where Kahn Tests are mentioned, the

technique was a two tube method containing antigen-serum mixtures of 1 in 12 and 1 in 6. The blood for the serological tests was obtained on the day that the diagnosis was made and treatment commenced. The tests were repeated at the beginning of the second course following the rest period. The second Wassermann Reaction was thus carried out in the thirteenth week after the beginning of treatment.

As a further comparison the follow-up on 160 cases of early syphilis treated with penicillin has been included. The cases in this group were diagnosed and treated by me in The Central Mediterranean Forces. Wassermann Reactions could not be obtained. Kahn tests only were carried out in this series.

Unit Course No. 1.

This course was that described by Prebble and consisted of twice weekly injections of neoarsphenamine and bismuth oxychloride (13). It extended over thirty nine days and a rest period of six weeks was given between courses. The number of cases treated in this way was 205.

Day	Neoarsphenamine	Bismuth Oxychloride
1	0.3g.	0.2g.
4	0.45g.	0.2g.
8	0.3g.	0.2g.
11	0.45g.	0.2g.
15	0.3g.	0.2g.
18	0.45g.	0.2g.
22	0.3g.	0.2g.
25	0.45g.	0.2g.
29	0.3g.	0.2g.
32	0.45g.	0.2g.
36	0.3g.	0.2g.
39	0.45g.	0.2g.

Total neoarsphenamine = 4.5g.

The group of 205 cases treated with this course was divided into four groups according to the clinical findings and the serological reactions before treatment, as follows:-

(a) Sero-negative primary syphilis.

(b) Sero-doubtful primary syphilis.

(c) Sero-positive primary syphilis.

(d) Secondary syphilis.

The results of the Wassermann Reaction performed during the thirteenth week after treatment was commenced, are tabulated below:-

(a) In 66 cases of Sero-negative primary syphilis:

	No.	Per cent.
Sero-positive	Nil	Nil
Sero-doubtful	Nil	Nil
Sero-negative	66	100

(b) In 11 cases of sero-doubtful primary syphilis:

	No.	Per cent.
Sero-positive	Nil	Nil
Sero-doubtful	Nil	Nil
Sero-negative	11	100

(c) In 90 cases of sero-positive primary syphilis:

	No.	Per cent.
Sero-positive	1	1.1
Sero-doubtful	4	4.4
Sero-negative	85	94.4

(d) In 38 cases of secondary syphilis:

	No.	Per cent.
Sero-positive	3	7.9
Sero-doubtful	3	7.9
Sero-negative	32	84.3

The total number of sero-positive and sero-doubtful cases was 139. The number of cases undergoing complete serological reversal was 128 or92% at the thirteenth week after the commencement of treatment.

The average incubation periods in groups (c) and (d) were calculated with a view to estimating whether reversal of the serological reaction of the blood was directly affected by the duration of the infection. The incubation periods are given below.

(c) In 90 cases of sero-positive primary syphilis, the results of the Wassermann Reaction at the 13th week of treatment and the incubation periods, were as follows:-

	Incubation period.
Sero-positive	42.0 days
Sero-doubtful	47.25 days
Sero-negative	43.82 days

(d) In 38 cases of secondary syphilis the results of the Wassermann Reaction at the 13th week of treatment and the incubation periods were as follows:-

Sero-positive	64.33 days
Sero-doubtful	55.33 days
Sero-negative	66.00 days.

Unit Course No. 2.

This course has already been described in detail in the introduction to this section, and was in routine use in the Army between 1942 and 1944. The total neoarsphenamine given was 4.05g. and the total bismuth oxychloride 2.5g. The course covered a period of 61 days and was followed by a rest period of four weeks before the second course. The results of the changes in the serological reactions as determined at the beginning of the second course in 129 cases are tabulated below:-

(a) In 38 cases of sero-negative primary syphilis:

	No.	Per cent.
Sero-positive	1	2.6
Sero-doubtful	5	13.0
Sero-negative	32	84.4

(b) In 9 cases of sero-doubtful primary syphilis:

	No.	Per cent.
Sero-positive	Nil	Nil
Sero-doubtful	1	11.0
Sero-negative	8	89.0

(c) In 51 cases of sero-positive primary syphilis:

	No.	Per cent.
Sero-positive	2	2.0
Sero-doubtful	10	20.0
Sero-negative	39	78.0

(d) In 31 cases of secondary syphilis:

	No.	Per cent.
Sero-positive	5	16.0
Sero-doubtful	10	32.2
Sero-negative	16	51.2

The total number of sero-positive and sero-doubtful cases was 91. The number of cases undergoing complete serological reversal at the thirteenth week of treatment was 63 (69%).

Unit Course No. 3.

The third course in this study was as follows:-

Day	Neoarsphenamine	Bismuth Oxychloride
1	0.45g.	0.2g.
4	0.45g.	0.2g.
9	0.45g.	0.2g.
16	0.45g.	0.2g.
23	0.45g.	0.2g.
30	0.45g.	0.2g.
37	0.45g.	0.2g.
44	0.45g.	0.2g.
51	0.45g.	0.2g.
67	0.45g.	0.2g.

Total neoarsphenamine = 4.5g.

A group of 164 cases was treated with this unit course.

The results of the Wassermann Reaction performed on the thirteenth week after the commencement of treatment are analysed below.

(a) In 62 cases of sero-negative primary syphilis:

	No.	Per cent.
Sero-positive	2	3.2
Sero-doubtful	3	4.8
Sero-negative	57	91.2

(b) In 6 cases of sero-doubtful primary syphilis:

	No.	Per cent.
Sero-positive	Nil	Nil
Sero-doubtful	Nil	Nil
Sero-negative	6	1 00

(c) In 62 cases of sero-positive primary syphilis:

	No.	Per cent.
Sero-positive	5	8.0
Sero-doubtful	9	14.4
Sero-negative	48	76.8

(d) In 34 cases of secondary syphilis:

	No.	Per cent.
Sero-positive	6	17.6
Sero-doubtful	9	26.5
Sero-negative	19	55.9

Total sero-positive and sero-doubtful cases numbered 102. The number of cases undergoing complete serological reversal by the thirteenth week was 73 (71%).

Unit Course No. 4.

This course was similar to Course No. 3 except that after the initial dose of 0.45g. neoarsphenamine the subsequent nine injections of arsenic were 0.6g.

Day	Neoarsphenamine	Bismuth Oxychloride
1	0.45g.	0.2g.
4	0.6g.	0.2g.
9	0.6g.	0.2g.
16	0.6g.	0.2g.
23	0.6g.	0.2g.
30	0.6g.	0.2g.
37	0.6g.	0.2g.
44	0.6g.	0.2g.
51	0.6g.	0.2g.
67	0.6g.	0.2g.

Total neoarsphenamine = 5.85g.

171 cases were treated with this unit course. The results of the Wassermann Reactions performed on the thirteenth week after treatment was commenced are analysed below.

(a) In 64 cases of sero-negative primary syphilis:

	No.	Per cent.
Sero-positive	1	1.6
Sero-doubtful	2	3.2
Sero-negative	61	95.3

(b) In 5 cases of sero-doubtful primary syphilis:

	No.	Per cent.
Sero-positive	Nil	Nil
Sero-doubtful	Nil	Nil
Sero-negative	5	100

(c) In 64 cases of sero-positive primary syphilis:

	No.	Per cent.
Sero-positive	2	3.2
Sero-doubtful	2	3.2
Sero-negative	60	93.7

(d) In 38 cases of secondary syphilis:

	No.	Per cent.
Sero-positive	8	13.1
Sero-doubtful	5	21.0
Sero-negative	25	66.0

Total sero-positive and sero-doubtful cases numbered 107. Cases undergoing complete serological reversal at the thirteenth week after the beginning of treatment numbered 90 (84%).

Unit Course No. 5.

This course consisted of twice weekly injections of Mapharside and weekly injections of bismuth oxychloride.

Day	Mapharside	Bismuth Oxychloride
1	0.04g.	0.3g.
4	0.06g.	Nil
8	0.04g.	0.3g.
11	0.06g.	Nil
15	0.04g.	0.03g.
18	0.06g.	Nil
22	0.04g.	0.03g.
25	0.06g.	Nil
29	0.04g.	0.03g.
32	0.06g.	Nil
36	0.04g.	0.03g.
39	0.06g.	Nil

Total Mapharside = 0.6g.

Only a small group of 50 cases was treated with this unit course. The results of the Wassermann Reactions performed in the thirteenth week after treatment commenced are analysed below.

(a) In 20 cases of sero-negative primary syphilis:

	No.	Per cent.
Sero-positive	Nil	Nil
Sero-doubtful	Nil	Nil
Sero-negative	20	100

(b) There were no cases of sero-doubtful primary syphilis in this group.

(c) In 25 cases of sero-positive primary syphilis:

	No.	Per cent.
Sero-positive	Nil	Nil
Sero-doubtful	2	8
Sero-negative	23	92

(d) In 5 cases of secondary syphilis:

	No.	Per cent.
Sero-positive	Nil	Nil
Sero-doubtful	Nil	Nil
Sero-negative	5	100

Total sero-positive and sero-doubtful cases numbered 30. The number of cases undergoing complete serological reversal at the thirteenth week after commencing treatment was 28 (93%).

Unit Course No. 6.

Unit Course No. 6 lasted nine and a half weeks, during which 1.2g. of Mapharside were given in twice weekly doses of 0.06g. Weekly doses of 0.2g. of bismuth oxychloride were given in conjunction with the arsenic.

Day	Mapharside	Bismuth Oxychloride
1	0.06g.	0.2g.
4	0.06g.	Nil
7	0.06g.	0.2g.
10	0.06g.	Nil
14	0.06g.	0.2g.
17	0.06g.	Nil
21	0.06g.	0.2g.
24	0.06g.	Nil
28	0.06g.	0.2g.
31	0.06g.	Nil
35	0.06g.	0.2g.
38	0.06g.	Nil
42	0.06g.	0.2g.
45	0.06g.	Nil
49	0.06g.	0.2g.
52	0.06g.	Nil
56	0.06g.	0.2g.
59	0.06g.	Nil

Unit Course No. 6 (Continued).

Day	Mapharside.	Bismuth Oxychloride.
63	0.06g.	0.2g.
67	0.06g.	Nil

Total Mapharside = 1.2g.

A 100 cases were treated with this unit course as outlined and the results of the Wassermann Reaction carried out in the thirteenth week after treatment commenced, are analysed below.

(a) In 30 cases of sero-negative primary syphilis:

	No.	Per cent.
Sero-positive	Nil	Nil
Sero-doubtful	7	23.3
Sero-negative	23	76.6

(b) In 13 cases of sero-doubtful primary syphilis:

	No.	Per cent.
Sero-positive	3	23
Sero-doubtful	Nil	Nil
Sero-negative	10	76

(c) In 36 cases of sero-positive primary syphilis:

	No.	Per cent.
Sero-positive	Nil	Nil
Sero-doubtful	3	8.4
Sero-negative	33	91.6

(d) In 21 cases of secondary syphilis:

	No.	Per cent.
Sero-positive	1	4.7
Sero-doubtful	Nil	Nil
Sero-negative	20	95.3

The total sero-positive and sero-doubtful cases numbered 70. The number of cases undergoing complete serological reversal thirteen weeks after treatment was commenced, was 63 (90%).

Penicillin Schedule No. 1.

The total amount of penicillin administered to each case in this group was 2,000,000 Oxford Units of penicillin. One hundred injections of 20,000 Oxford Units were given at intervals of three hours for three hundred hours. Kahn Tests only were carried out at the beginning of treatment and at the thirteenth week. No other anti-syphilitic drugs were given. 52 cases were treated by this schedule and the results of the Kahn Tests are analysed below.

(a) In 23 cases of sero-negative primary syphilis:

	No.	Per cent.
Sero-positive	Nil	Nil
Sero-doubtful	Nil	Nil
Sero-negative	23	100

(b) In 4 cases of sero-doubtful primary syphilis:

	No.	Per cent.
Sero-positive	Nil	Nil
Sero-doubtful	Nil	Nil
Sero-negative	4	100

(c) In 15 cases of sero-positive primary syphilis:

	No.	Per cent.
Sero-positive	3	20
Sero-doubtful	Nil	Nil
Sero-negative	12	80

(d) In 10 cases of secondary syphilis:

	No.	Per cent.
Sero-positive	4	40
Sero-doubtful	Nil	Nil
Sero-negative	6	60

The total number of sero-positive and sero-doubtful cases was 29. Cases undergoing complete serological reversal at the thirteenth week after the beginning of treatment numbered 22 (75.8%).

In this series, twenty cases were followed up for a period of six months. Kahn Tests were negative in 18 cases as were the findings in the cerebro-spinal fluid when examined at six months. Two of the cases relapsed and were retreated.

Penicillin Schedule No. 2.

In this schedule the total amount of penicillin administered was 2,400,000 Oxford Units. 30,000 Oxford Units were given every three hours for a period of ten days. Kahn Tests were carried out at the beginning of treatment and at the thirteenth week after the beginning of treatment. No other anti-syphilitic drugs were given. The results of the Kahn Tests in 108 cases are analysed below.

(a) In 56 cases of sero-negative primary syphilis:

	No.	Per cent.
Sero-positive	2	3.6
Sero-doubtful	Nil	Nil
Sero-negative	54	97.2

(b) In 9 cases of sero-doubtful primary syphilis:

	No.	Per cent.
Sero-positive	Nil	Nil
Sero-doubtful	1	11.1
Sero-negative	8	88.8

(c) In 33 cases of sero-positive primary syphilis:

	No.	Per cent.
Sero-positive	6	18.3
Sero-doubtful	3	9.3
Sero-negative	24	72.3

(d) In 10 cases of secondary syphilis:

	No.	Per cent.
Sero-positive	2	20
Sero-doubtful	Nil	Nil
Sero-negative	8	80

The total number of sero-positive and sero-doubtful cases was 52. The number of cases undergoing complete serological reversal thirteen weeks after treatment was commenced was 40 (76.9%).

In this series of cases 64 were followed up for a minimum period of six months. Ten cases relapsed and were retreated during this period.

A graph showing the percentage of cases undergoing complete serological reversal thirteen weeks from the commencement of treatment with the various courses and schedules described above is attached.

Graph No.3. Shows the percentage of complete serological reversal achieved 15 weeks after treatment was commenced with various unit courses and with penicillin.

Course 1. Course 2. Course 3. Course 4. Course 5. Course 6. Schedule 1. Schedule 2

2,400,000 Oxford Units of penicillin in 300 hours.

2,000,000 Oxford Units of penicillin in 300 hours.

Total mapharside = 1.2g.
Injections given twice weekly.

Total mapharside = 0.6g.
Injections given twice weekly.

Total neoarsphenamine = 5.85g.
Injections given weekly.

Total neoarsphenamine = 4.5g.
Injections given weekly.

Total neoarsphenamine = 4.05g.
Injections given weekly.

Total neoarsphenamine = 4.5g.
Injections given twice weekly.

100 90 80 70 60 50 40 30 20 10 0

percent.

DISCUSSION.

1. For the purposes of this study, patients suffering from primary or secondary syphilis were alone included. Any patient who, for whatever reason, failed to receive his allotted treatment according to schedule, was excluded from the series. In every other respect the cases were unselected. In all, the groups treated with neoarsphenamine total 819 cases, and 160 cases were treated with penicillin, a total of 979 cases.

2. As stated, the blood for serological tests was taken on the day treatment was commenced and again thirteen weeks later; the tests were performed in the same laboratory and under comparable conditions.

3. The table below presents the percentage composition of sero-negative and sero-positive cases for each group of patients treated by the various unit courses. For this purpose sero-doubtful results are included with sero-negative reactions. With the exception of Group No. 5 it will be noted that the percentage of sero-negative and sero-positive cases in each group is relatively constant. It is reasonable therefore to use these groups for comparing the sero-reversal obtained by the unit courses described.

Unit Course	No.1	No.2	No.3	No.4	No.5	No.6
% of sero-negative and sero-doubtful cases	37.3	36.9	41.4	40.0	50.0	43.0
% of sero-positive cases.	62.5	68.1	58.6	60.0	50.0	57.0

4. Graph No.3 shows the percentage of serological reversal in the groups of cases treated with Unit Courses Nos. 1 to 6. In Courses Nos. 1 and 3 the total weight of arsenic administered is the same, consisting of one injection twice weekly for six weeks (12 injections) in Course No. 1 while in Course No. 3 it is administered in ten injections at weekly intervals. Course No. 1 resulted in 92% of sero-reversal while Course No. 3 only achieved 71%.

5. Courses Nos. 3 and 4 both comprised ten injections of neo-arsphenamine at weekly intervals but in Course No. 3 the total weight administered was 4.5g. of neoarsphenamine while in Course No. 4 the total weight was 5.85g. Serological reversal in the latter was 84% while in Course No. 3 sero-reversal occurred in only 71% of cases.

6. In Courses No. 1 and No. 2 in which the arsenic and bismuth are almost identical serological reversal occurred in 92% treated by Course No. 1 and 69% treated by Course No. 2. This difference suggests strongly that arsenical injections are therapeutically more effective when administered at regular intervals without intermissions as occured in Course No. 2 at the 4th, 6th and 8th weeks of treatment.

7. Only one conclusion is justifiable from a study of the results obtained by Courses Nos. 5 and 6 in view of the fact that the composition of Group 5 is not comparable with the other groups, namely, that equally good results as judged by serological reversal are obtainable by the use of mapharside.

8. It will be noted that in Courses Nos. 3 and 4 the bismuth factor is identical both in regard to total dosage, number and intervals of injections. This factor is not identical in Unit Courses Nos. 1 and 3. It would of course have been ideal to eliminate bismuth entirely from all these treatment courses, but such a step was not practical in the present investigation. Bismuth being an insoluble drug forming on injection, a depot in the muscles from which regular absorption takes place, the difference may reasonably be discounted.

9. Schedules 1 and 2 comprise 160 cases of primary or secondary syphilis. With the exception of the total number of penicillin units administered the results in Schedules 1 and 2 are strictly comparable.

CONCLUSIONS.

Judged from the complete reversal of the serological reaction 13 weeks after treatment was commenced:-

1. Using weight for weight of neoarsphenamine a higher percentage of serological reversal is obtained by giving the drug twice weekly rather than once weekly. (See Discussion para. 4)
2. The percentage of cases achieving complete serological reversal is proportional to the weight of neoarsphenamine administered. (See Discussion para. 5)
3. Neoarsphenamine should be administered at regular intervals without intermissions to achieve a high percentage of serological reversal. (See Discussion para. 6)
4. Satisfactory results in the reversal of the serological reaction can be obtained with mapharside.
5. A total dosage of 2,400,000 Oxford Units of penicillin is not adequate treatment for all cases of primary and secondary syphilis. As there is no significant difference obtained in serological reversal by 2,400,000 Oxford Units as compared with 2,000,000 Oxford Units given over the same period (300 hours) it will probably be necessary not only to increase the total dosage of penicillin but also to consider the importance of the "time/dosage" factor.

S E C T I O N III.

SECTION III.

A STUDY OF THE MAJOR REACTIONS TO TRIVALENT ARSENICAL COMPOUNDS AND AN INVESTIGATION INTO NEW METHODS OF MANAGEMENT OF THESE REACTIONS.

I N T R O D U C T I O N.

Major reactions arising from arsenotherapy postpone the completion of adequate treatment and prejudice the prognosis in cases of early syphilis. Also, in civil practice, these reactions encourage default and add to the difficulties of case-holding. These disadvantages are perhaps less important now that penicillin is available but still remain significant.

Such reactions to treatment may follow the use of the trivalent arsenical preparations and are here divided into two groups according to their aetiology and management.

GROUP I: Jaundice; excluding icterus associated with Milian's erythema of the 9th day.

GROUP II: (a) Milian's syndrome of erythema of the 9th day.
(b) Haemorrhagic encephalopathy.
(c) Agranulocytosis.
(d) Aplastic anaemia.
(e) Arsenical purpura.
(f) Dermatitis (excluding exfoliative dermatitis).
(g) Exfoliative dermatitis.

It will be shown that the jaundice mentioned in Group I being of infective origin, can be prevented. Generalised

dermatitis with exfoliation is dealt with separately because a new method of management, as compared with the other reactions in this group, has been studied.

The incidence of many of the reactions in Group II may be reduced by attention to detail in the choice, preparation and administration of the arsenical preparations combined with alertness in detecting the prodromata which may herald their appearance. Thus sulpharsphenamine is known to be followed more often by blood dyscrasias and dermatitis than is the case with neoarsphenamine. Again, in addition to using a batch of drug well within the manufacturer's expiry date, care must be taken to avoid oxidation both in its preparation and by immediate administration. It is a sine qua non that the injection must be wholly intravenous and no perivenous leak permitted. Warning of impending dermatitis and blood dyscrasias may be obtained by careful questioning and examination of the patient before each injection.

Hitherto, many of these cases have been regarded as unsuitable for further treatment with the trivalent arsenical drugs. In this section a method will be described whereby such treatment can be quickly resumed.

GROUP I.

Jaundice; excluding icterus associated with Milian's erythema of the 9th day.

Introduction.

Jaundice has been recognised as occurring in the course of syphilis for at least four centuries. Following the introduction of the arsenical compounds by Erlich in 1910, jaundice occurring during treatment with these drugs has been more frequently reported under the title of post-arsphenamine jaundice, as it was thought to be a toxic effect on the liver cells.

Since the 1914 - 18 War there have been epidemics from time to time, all over the world, of what has been termed catarrhal jaundice but which now would be termed infective hepatitis, since epidemiological studies and experimental investigation have proved that the condition is infective in origin and probably spread by droplet infection. (22, 71, 72). Until the 1939 - 45 War the incidence of post-arsphenamine jaundice was generally reported as being less than 0.2% (15) although in one paper an incidence of 50.18% was given. (29).

Epidemiological studies suggest that infective hepatitis has an incubation period of from three to five weeks. It is spread by droplet infection during close but not necessarily prolonged contact and occurs most frequently in children and young adults. One attack confers immunity on the individual and second attacks are rare (72). Homologous serum jaundice occurs after the injection of pooled plasma, whole blood,

convalescent serum and yellow fever vaccine (17, 18, 19, 21). It has an incubation period of from two to four months and cannot be differentiated pathologically or clinically from infective hepatitis although it has been pointed out by Hawley (19) that homologous serum jaundice may be associated with a greater incidence of allergic phenomena.

Post-arsphenamine jaundice occurring during the treatment of syphilis with the arsphenamines may be divided into two types. The first occurs during the seven to fourteen days following the first injection of arsenic and is probably an allergic phenomenon associated with Milian's syndrome of the 9th day. This type will be discussed later. The second variety has an incubation period of from two to four months and is indistinguishable clinically and pathologically from infective hepatitis (20,21,22). It is this latter, more common variety which is considered in this section.

Theoretically post-arsphenamine jaundice may be due to four causes:-

1. To syphilis.
2. To the direct or indirect action of the organic arsenical preparations used in treatment.
3. To an infective agent.
4. To any combination of the above three causes.

1. Jaundice occurs as a rarity during the course of untreated syphilis and clears up quickly with specific treatment. (5, 15) The incidence in different clinics would not vary so widely as from 0.1% to 50% nor would it occur after a period of treatment varying from ten to eighteen weeks.

2. It is well recognised that arsenic is detoxicated in the liver and many have assumed that post-arsphenamine jaundice was due to liver damage arising from the arsenic. It has been shown that hepatitis can be produced in animals by large doses of the arsphenamines. The dose, however, is far beyond the therapeutic level (26). The incidence of post-arsphenamine jaundice is independent of the preparation used and within the therapeutic limits independent of the dosage, also the incidence varies from clinic to clinic and from time to time in the same clinic although the drugs and dosage used remain constant (73). It is considered therefore that arsphenamine per se has little, if any effect on the incidence of post-arsphenamine jaundice.

It has been shown experimentally that the liver can be protected from damage by the arsphenamines by diet and that certain aminoacids, particularly methionine, protect the liver from chloroform in protein depleted dogs (23, 26). Beattie and Marshall have reported on the prevention and treatment of post-arsphenamine jaundice with methionine with rather inconclusive results (24). Darmady has reported on the treatment of infective hepatitis with a high protein diet with similar results (25). The reduction of protein in the diet during the 1939 - 45 War is unlikely to be a significant factor as the

incidence of this complication has been reported as 50% in a clinic in 1934 (29). It is considered that while diet may play a part in the aetiology of post-arsphenamine jaundice, it is an unimportant factor.

3. In early 1943 MacCallum (27) and Biggar (28) suggested that jaundice might be caused by an infective agent passed from patient to patient via the syringes used in intravenous treatment. Biggar drew attention to the fact that in many venereal disease clinics, syringes were few and were not adequately sterilised between each injection. A common practice was to boil the syringe at the beginning of each out-patient session only, or even to omit this, the syringe being left in spirit for twenty four hours prior to the session. The practice was to first wash out the syringe in an antiseptic fluid and then in sterile water between each injection. Biggar showed by bacteriological experiments using staphylococci that these methods were insufficient to rid the syringe of bacterial contamination. Frequent washings did not remove all bacteria from the syringe, many lodging around the head of the plunger.

Ruge (16) has shown from epidemiological data from the German Navy between 1918 and 1930 that the rise in incidence of post-arsphenamine jaundice was almost parallel to that of infective hepatitis.

Logically, the hypothesis that post-arsphenamine jaundice might be due to the virus of infective hepatitis, syringe transmitted, arose following Biggar's work. In the summer of 1943 Col. Sheehan, Deputy Director of Pathology, Western Command

collected evidence to support this hypothesis. His evidence briefly was as follows:-

(a) In 80 female patients treated in a clinic in which syringes were immersed in strong antiseptic solution for fifteen minutes between each injection, only two patients developed jaundice. It is probably significant that both these patients received some of their injections in another clinic.

(b) In a male clinic with a current incidence of jaundice of about 75%, five patients received all their injections with carefully sterilised syringes and meticulous precautions were taken to prevent contamination of these patients with blood from others. These five cases were observed for periods varying from 15 to 27 weeks and none developed jaundice.

(c) In a prisoner of war camp 34 cases were receiving anti-syphilitic treatment. It happened that these cases were treated in two groups. One group was treated on a Wednesday and the other on a Friday. The allocation of patients to either group was fortuitous but once started in a particular group the patient remained in it throughout his subsequent treatment. Apart from the one variable factor of the day of treatment all other dietetic, environmental, drug and dosage factors were identical. Syringes were sterilised by boiling at the beginning of the clinic on Wednesday and on Friday but were only washed out between each injection in the group. There was thus an opportunity for transmitting a blood borne infection among members of one group but not of transmitting infection from one group to the other. One

patient, introduced into the Wednesday group, had received anti-syphilitic treatment elsewhere and was already developing hepatitis. In due course he developed jaundice. Subsequently eight other men in the Wednesday group developed hepatitis but the patients in the Friday group remained free.

(d.) Over a period of twelve months, three special treatment orderlies employed in a syphilis clinic, who from time to time had their hands contaminated with blood from the patients, developed typical hepatitis. Again, three laboratory assistants engaged in separating serum for serological tests from the blood of patients under treatment, developed hepatitis. None of these six cases had received any arsenical injections nor had they received any inoculations with unsterile syringes. During this period of twelve months cases of post-arsphenamine jaundice in the clinic were frequent. It is possible that infection gained entrance through small abrasions in the skin of their hands.

(e) Small out-breaks of jaundice have been recorded in the past amongst groups of patients subjected to venepuncture; e.g. in a diabetic clinic, in a clinic for rheumatoid arthritis where gold salts were administered and in a sanatorium where monthly estimations of the blood sedimentation rate were performed. In the light of recent knowledge it seems probable that these were all examples of infective hepatitis spread by syringes contaminated with ictero-genic serum.

Following consideration of this evidence, Major Laird, Command Specialist in Venereology, Western Command, applied for

War Office authority to carry out a special investigation at a Military Hospital. He stipulated that this investigation could only be carried out if the following conditions were guaranteed:-

1. A special centre should be designated to perform the research.
2. One Medical Officer should be placed in sole charge of the work and should not be posted until the trial had been completed. A specially selected and trained team should be given similar security of tenure.
3. The number of syringes and needles and the facilities for their sterilisation by boiling must be adequate.
4. The patients treated in this centre must <u>not</u> receive any injections or have blood taken for serological tests elsewhere. This meant that treatment must be initiated and maintained for at least six months at this special centre, even immunisation and vaccination must not be undertaken elsewhere.
5. Authority must be obtained for such patients to be attached to units in the vicinity of the special treatment centre and they must not be posted thence for at least six months.

In view of the importance attached to the investigation of post-arsphenamine jaundice, authority to fulfil these conditions was granted and I was placed in charge of the work, being responsible for the training of the team and supervision of the technique. All intravenous injections were given personally.

The object of the Investigation.

The investigation was undertaken to test the hypothesis that post-arsphenamine jaundice was caused by a virus infection passed from patient to patient by contaminated syringes. Direct proof of this hypothesis was not practical, but it was believed that if the incidence of post-arsphenamine jaundice which was then approximately 50% could be greatly reduced by the use of a special technique in intravenous injection which prevented the transfer of blood and serum from one patient to another, then this could be interpreted as indirect proof of the hypothesis, provided all other environmental, dietetic and therapeutic factors were constant. The special technique had, preferably, to be one which could be carried out in any clinic provided the staff and materials were adequate.

A Detailed Description of the Investigation.

The investigation was carried out in the syphilis out-patient department of a Military Hospital, and the soldiers included in the investigation were all cases of primary or secondary syphilis in whom the diagnosis had been established by dark-ground examination of serum from a primary or secondary lesion. All injections, inoculations and vaccinations were carried out in the clinic using a similar technique to that described below. The anti-syphilitic treatment given was the standard course employed as a routine for early syphilis and was as follows:-

Day	Neoarsphenamine.	Bismuth Oxychloride.
1	0.45g.	0.2g.
4	0.6g.	0.2g.
9	0.6g.	0.2g.
16	0.6g.	0.2g.
23	0.6g.	0.2g.
30	0.6g.	0.2g.
37	0.6g.	0.2g.
44	0.6g.	0.2g.
51	0.6g.	0.2g.
58	0.6g.	0.2g.

The second, and subsequent courses, were identical with the first. A rest period of four weeks was given between courses and blood for a Wassermann Reaction was taken at the beginning of each course prior to the first injection of neoarsphenamine in the course. The same proprietary preparations of neoarsphenamine and bismuth were used throughout the investigation.

During the first two weeks of their treatment, the soldiers included in this investigation mingled with other patients in the syphilis wards, including patients suffering from post-arsphenamine jaundice. Later, as out-patients, they were in contact, in the out-patients department, with others who were incubating post-arsphenamine hepatitis. All patients were given their injections in the order in which they arrived at the out-patient department and the same syringes were used for all patients receiving treatment whether or not they were included in

the investigation.

Every patient in the investigation was observed over a minimum period of 180 days and the majority were observed for longer.

The risk of transmitting infection by intramuscular injection was considered to be less but the possibility was investigated. The first five patients treated were given their bismuth injections with a boiled needle and syringe and full precautions against contamination with blood or serum were taken. The second five patients were given their bismuth with a sterile needle and the syringe normally used for bismuth injections. This syringe was boiled only at the beginning of each session. Alternative groups of five patients in the investigation were treated similarly.

As already stated blood for serological testing was taken at the beginning of each course. The venepuncture was performed under the same conditions as those laid down for the injection of neoarsphenamine.

A Detailed Description of the Technique Used in Treatment.

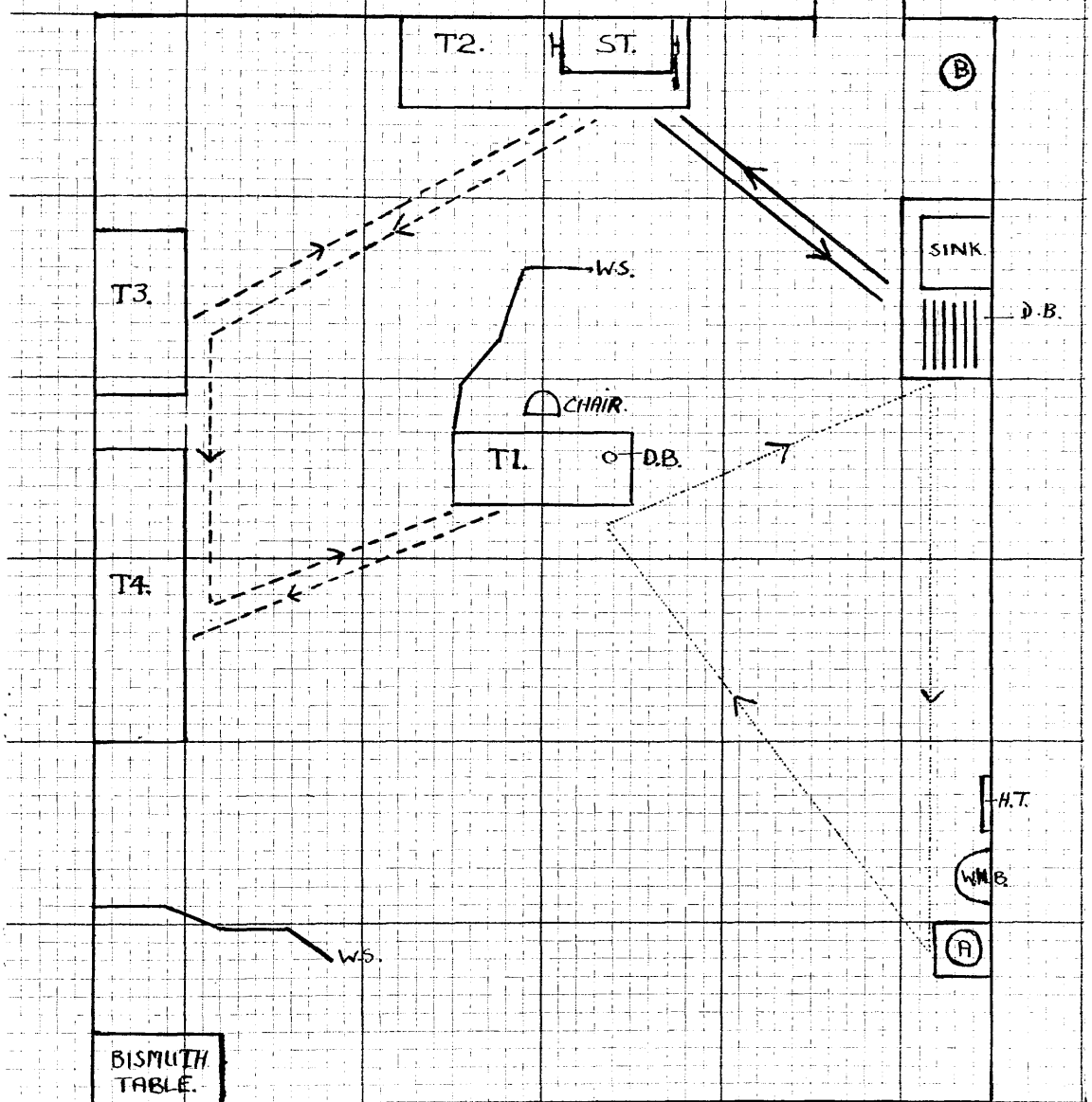
The object of this technique is to prevent contamination with blood or serum of one patient and the next, and the basic principles are those used in the "bed isolation" of infectious cases, with all materials, equipment and staff in a "clean" or "contaminated" state. Diagram I shows the lay-out in the syphilis out-patient department and the routes taken by each member of the team of three, comprising one Medical Officer and two special treatment orderlies.

DIAGRAM I

T1. Injection Table.
T2. Table with steriliser.
T3. Table for steriliser tray with sterile syringes.
T4. Table for preparing injections.
W.H.B. Wash hand basin used by M.O.
D.B. Draining-board to sink.
A. Bowl of 1:40 carbolic lotion.
H.T. Hand towel for use of M.O. only.
W.S. Ward screens.
B. Bucket for contaminated swabs.

..... Route taken by M.O.
- - - - Route taken by uncontaminated orderly.
——— Route taken by contaminated orderly.

Patients' entrance and exit.



One of the orderlies handles only contaminated equipment and the other uncontaminated equipment. Any article which has been in contact with a patient is automatically considered to be contaminated whether or not it has been in contact with blood or serum. The Medical Officer is the only member of the team who handles both contaminated and uncontaminated material and equipment, and he decontaminates himself between each injection.

The "contaminated Orderly" washes out syringes and needles at the sink (see diagram) and checks the needles for patency and sharpness. He wraps each washed syringe and plunger in a large square of lint. The size of this square is important. It must be large enough to cover the breadth of the injection table (T.1) and fall about two inches over each side. When a number of syringes and needles have been washed and wrapped, the syringes separately and the needles in one packet of lint, the "contaminated orderly" places them in the steriliser (St.) on table No. 2 (T.2), lowers the tray and switches on the current. When the contents have boiled for 20 minutes he switches off the current, lifts the lid, raises the tray by means of the lever on the steriliser and leaves the contents to cool. He does not touch the handles of the tray or the boiled syringes and needles. The lint squares are re-used many times. Should they become contaminated with blood the orderly washes them out with soap and water at the sink.

The "clean" or "uncontaminated orderly" lifts the tray containing the syringes and needles out of the steriliser and places them on a table (T.3). He unwraps the syringes in a

large enamel tray previously sterilised by flaming, and assembles the plungers and barrels on one half of the tray. The squares of lint are placed on the other half of the tray. He prepares the injection in a sterile galley-pot, previously sterilised by boiling, loads the syringe and attaches the needle, using sterile Cheatle's forceps. He then holds out by forceps, a square of lint and the Medical Officer takes this without touching the forceps and lays it over the injection table. The patient seats himself on the chair in front of the injection table, lays his arm on the lint square and distends the veins of his forearm by compressing his arm manually. The Medical Officer who has not yet touched the patient drops some spirit on the arm from the drop-bottle (D.B.). The "uncontaminated orderly" places the syringe and needle containing the arsenical injection on to the square of lint without touching the lint, Medical Officer or patient. The Medical Officer takes the syringe and gives the injection. Meanwhile the "uncontaminated orderly" has dropped a sterile swab of cotton wool on to the lint square. The patient presses this on his arm over the site of the injection and holding his arm above his head leaves his seat and goes to the bucket for contaminated swabs (B.). When he is sure that all oozing from the venepuncture has ceased he drops the swab into the bucket. The Medical Officer meanwhile lifts the contaminated syringe and lint and places them on the draining board (D.B.). He then goes to the wash-hand basin (W.H.B.) and washes his gloved hands thoroughly in running water using soap. Following this he soaks his hands in the basin (A.) which

contains 1:40 carbolic solution for a full minute. After drying his hands on the hand towel (H.T.), which he alone uses, he is ready to proceed with the next injection.

It was found in practice that if a few minutes were taken to explain to the patient the "dos" and "don'ts" before his first injection, no time was wasted and the patients co-operated well.

All injections were given with large bore hypodermic needles and the distance between the points of entry into the skin and into the vein was at least $\frac{1}{4}$ inch. This achieved the important object of reducing the amount of leak from the venepuncture to a minimum. Care was taken to keep the rubber gloves and gown of the Medical Officer as free from contamination as possible and the decontamination process was rigorously carried out. It will be obvious that this technique of injection completely breaks the contact between one patient and the next. The gown and gloves of the Medical Officer were, of course, unsterile, the object of the technique being to break the contact between patients rather than to give injections under full aseptic conditions.

The method lends itself to team work and organisation and in practice with a well trained team and sound intravenous technique, 30 patients can be treated per hour, provided the sterilisation has been done previously and the "uncontaminated orderly" has a list of the drugs and doses which are to be given. While the Medical Officer is decontaminating his gloved hands the next injection to be given is being prepared. Each alternate group of five patients receiving their bismuth from a freshly boiled syringe, are given the injection by the "uncontaminated orderly", who scrubs his hands in soap and water before and after

each injection.

The Results Obtained from the Investigation.

102 patients were treated using this technique and followed up for a period of 180 days or longer. Only one patient developed jaundice.

DISCUSSION.

1. Shortly before this technique was adopted I carried out an evaluation of the relative merits of neoarsphenamine and mapharside. Alternate patients suffering from primary or secondary syphilis were given neoarsphenamine and mapharside, all the injections being given in my out-patient department. These patients were followed up for a minimum period of 15 weeks after the first injection of arsenic and the incidence of jaundice occurring during these 15 weeks was as follows:-

   83 patients received mapharside; 42% developed jaundice.
   71 patients received neoarsphenamine; 43% developed jaundice

   It was noted in cases in which the follow-up of these patients was longer that the incidence still increased after the 15th week. It can therefore be concluded that the current incidence in the clinic was at least 42%.

2. During the year that this investigation was carried out there were 44 cases of jaundice admitted to my wards from the out-patient department. All these cases had received injections at other centres and 23 had received injections at my out-patient department while incubating hepatitis. It is apparent therefore, that infectious cases were introduced into the clinic during the period of this investigation.

3. During this year 99 patients, who commenced treatment at my department and were subsequently transferred to other centres were followed up for 180 days. 24 of these cases developed

hepatitis, the period between the last injection and the appearance of jaundice varying from 66 to 164 days. As the incubation period is usually about 60 to 70 days it is assumed that these patients were infected after leaving my clinic.

4. A further 65 cases, commencing treatment at this centre and treated according to the special technique and later treated at another centre using the same technique, remained free from jaundice for at least 180 days in all cases.

5. Laird (5) has investigated an out-break of post-arsphenamine jaundice at a centre where allneedles and syringes were sterilised by boiling but no organised method to prevent decontamination was in use. He concluded that the jaundice occurring during treatment was probably syringe transmitted and subsequent changes devised to eliminate all possibilities of contamination resulted in the elimination of jaundice.

6. Anwyl-Davies (29) has noted that in a clinic where the rate of hepatitis following the administration of neoarsphenamine was more than 50%, that boiling syringes and needles between each injection did not reduce the incidence of jaundice.

7. I noted that in a civilian clinic in which I worked during the time of this investigation that the incidence of jaundice was less than 1% although syringes were not boiled between each injection. It may be concluded that until the icterogenic substance is introduced into the clinic, no jaundice will occur even if the syringes are not boiled and contamination between patients occurs.

8. I have noted from records and personal observation that

when jaundice occurs in a treatment centre that the incidence increases in a "snow-ball" manner unless precautions to prevent syringe transmission and other contamination are introduced.

9. In 1942 the routine treatment for primary and secondary syphilis was changed so that the total weight of neoarsphenamine was reduced. This measure failed to arrest the steady rise in the incidence of post-arsphenamine jaundice.

CONCLUSIONS.

It is concluded that:-

1. Post-arsphenamine jaundice is an infective hepatitis indistinguishable from epidemic infective hepatitis and its spread amongst patients receiving arseno-therapy can be prevented by the introduction and operation of the use of a technique incorporating the principles described above.
2. The boiling of syringes and needles between each injection will not prevent the transfer of the icterogenic substance. Further precautions are necessary.
3. Infective hepatitis may occur in any clinic where numerous venepunctures are performed, provided that the infective agent is introduced and that the technique is such as to allow of the transmission of serum from one patient to another.
4. While transfer of an icterogenic substance between patients receiving intramuscular injections may occur, this is less likely than where venepuncture is being repeatedly performed.

GROUP II.

INTRODUCTION.

A group of major reactions to the trivalent arsenical drugs have been considered together because they probably have a common aetiology. As already stated, the management of exfoliative dermatitis has been different from that of the other reactions in this group, although its aetiology is probably similar. The reactions considered in this group are as follows:-

(a) The syndrome of Milian's erythema of the 9th day.

(b) Haemorrhagic encephalopathy.

(c) Agranulocytosis.

(d) Aplastic anaemia.

(e) Arsenical purpura.

(f) Dermatitis (excluding exfoliative dermatitis).

(g) Exfoliative dermatitis.

It has been recorded in the literature and noted in my own practice that this group of reactions may follow the use of the trivalent arsenical drugs, the sulphonamides and to a lesser degree gold preparations and thiouracil; the common factor being the benzene ring present in all the above mentioned drugs. It is not sufficiently realised that all these reactions may follow the use of any one of the drugs and are clinically identical irrespective of the offending substance.

Thus Park and Platts (32) among others have described a syndrome which occurs characteristically some 7 - 10 days after the commencement of sulphonamide therapy. This syndrome is receiving increasing recognition and is similar to 9th day

erythema (Milian's syndrome) which may occur after the use of the trivalent arsenicals. Sulphonamide therapy has been complicated by severe dermatitis (33, 34, 35 and 36), agranulocytosis (46). acute haemolytic anaemia (38), encephalopathy (37), and purpura (47). Again, following the use of gold therapy and thiouracil, agranulocytosis and dermatitis have been reported (67).

The consensus of opinion is that all these reactions can only be explained on the basis of allergy. With this hypothesis in mind Tate and Klorfajn (33, 34) have attempted the desensitisation of patients who have suffered from sulphonamide dermatitis, with success in some cases. In addition Park (46) has desensitised a case of agranulocytosis arising from sulphapyridine.

Gruhzit and Dixon (39), Leifer, Chargin and Hymen (40), Levin and Keddie (41), Anwyl-Davies (29) and others have reported that mapharside in equivalent therapeutic doses is less toxic than the arsphenamine group of drugs and causes fewer reactions. Cole and Palmer (42), Jordan and Traenkle(43), and Astrachan and Wise (44) have found that mapharside has been well tolerated in some cases in which toxic reactions to the arsphenamines have occurred.

Schooh, Alexander and Long (45) have reported on the results of desensitisation with mapharside after arsphenamine dermatitis.

In view of the above, it was considered logical to attempt the desensitisation of patients exhibiting the reactions in this group, using mapharside. The commencing dose was a very small one (0.001g.) and was increased subsequently, in the absence of

fresh evidence of intolerance, to a therapeutic level.

(a) The Syndrome of Erythema of the 9th Day.

Milian first described this reaction to arsphenamine in 1917. He termed it erythema of the 9th day and considered that it was due to a latent non-syphilitic infection stimulated by the administration of arsphenamine.

In 1941 Peters (48) from a study of 54 cases at the Johns Hopkins Clinic pointed out that the reaction occurs between the 5th and 9th days following the first injection of a trivalent arsenical. The rash is polymorphic, erythematous, scarlitiniform or macular and is accompanied by fever, malaise, headache, sore throat, nuchal rigidity, diarrhoea and enlargement of the superficial lymphatic glands. It occurs more frequently in women than in men and may be associated with nephritis, hepatitis or hepatomegaly without icterus, occurring just after the appearance of the rash. Peters showed that if treatment with the trivalent arsenicals was resumed within two weeks of the reaction 77% of patients developed a permanent intolerance to arsenic. If however treatment with the arsenicals was delayed for 1 - 2 months subsequent reactions were mild and occurred in only 28% of cases. The whole clinical syndrome is similar to that which occurs after the administration of the sulphonamides and, as with the sulphonamides, I have found that it is often associated with an eosinophilia.

The case-records and subsequent treatment of nine cases of this syndrome following the administration of neoarsphenamine

and occurring in my wards, are given below. All cases were males, and in none could a history of previous allergic states be elicited.

For the sake of brevity and for consideration of space the records given below are brief and consist of positive findings only, except where negative findings are deemed to be of importance.

Case No. 1.

Male aged 30 years. Diagnosis: Secondary syphilis.

This patient was admitted to hospital with a chancre on his prepuce, moist lesions on the perineum and scrotum, condylomata lata around the anus and specific ulceration of both tonsils. On admission, dark-ground examination of serum from his chancre and moist lesions was positive for T. pallidum and the Wassermann Reaction was reported as strongly positive.

On 24.9.44 he was given 0.45g. neoarsphenamine and 0.2g. bismuth oxychloride. This was followed by 0.6g.neoarsphenamine and 0.2g. bismuth oxychloride three days later and repeated after another five days.

On the tenth day after the first injection of neoarsphenamine an erythematous rash appeared on the trunk and limbs with macules on the extensor surfaces of the legs. The temperature rose to 104 deg. F. and subsided in forty eight hours. There was some nuchal rigidity, the lymphatic glands in the neck and axillae were palpable and the glands in the groin slightly enlarged. The epitrochlear glands were not palpable and there was no diarrhoea.

The White blood count was 11,600 per c.mm.

Differential W.B.C:

Polymorphonuclear neutrophils		79%
Eosinophils	...	1%
Basophils	...	0%
Large Lymphocytes	...	3%
Small Lymphocytes	...	13%
Large mononuclears	...	4%

The rash slowly faded, the skin returning to normal in four days. Two days later desensitisation using mapharside was commenced. A summary of treatment is given below:-

24.9.44.	0.45g. neoarsphenamine.	0.2g. bismuth oxychloride.
27.9.44.	0.6g. neoarsphenamine.	0.2g. bismuth oxychloride.
2.10.44.	0.6g. neoarsphenamine.	0.2g. bismuth oxychloride.
4.10.44.	Erythema of the 9th day.	
8.10.44.	Rash gone. Temperature normal.	
10.10.44.	0.001g. mapharside.	0.2g. bismuth oxychloride.
13.10.44.	0.002g. mapharside.	
14.10.44.	0.004g. mapharside.	
16.10.44.	0.01g. mapharside.	0.2g. bismuth oxychloride.
17.10.44.	0.02g. mapharside.	
21.10.44.	0.04g. mapharside.	
25.10.44.	0.06g. mapharside.	0.2g. bismuth oxychloride.

Treatment with mapharside, 0.06g. being given twice weekly, was co ntinued thereafter without further reaction.

Case No. 2.

Male aged 22 years. Diagnosis: Primary syphilis.

The patient was admitted to hospital on 8.5.44. He had a phimosis with a thick subpreputial discharge and bilateral inguinal adenitis. There was no urethral discharge and the urine contained no threads. A sore could be felt on the left side of the penis below the foreskin. On retracting the foreskin as far as possible, the edge of the sore could be seen. Treponema pallidum was seen on dark-ground examination of serum from the sore. The Kahn Test was negative. Treatment was commenced on 21.4.44 with 0.45g. neoarsphenamine and 0.2g.bismuth oxychloride. On 24.4.44 he was given 0.6g. neoarsphenamine and 0.2g. bismuth oxychloride and on 28.4.44 he complained of slight headache and malaise.

On 29.4.44 an erythematous and macular rash appeared on the back, loins, the extensor surfaces of both wrists, over the right knee and on the dorsum of both feet. He complained of nausea, headache and slight sore throat. The temperature rose to 100.2 deg. F. There was no nuchal rigidity or diarrhoea.

The white blood count was 12,200 per c.mm.

Differential white blood count:

Polymorphonuclear neutrophils	55%
Eosinophils	5%
Basophils	0%
Large lymphocytes ...	6%
Small lymphocytes ...	31%
Large mononuclears ...	3%

The serum bilirubin was less than 0.2mg. per 100 cc. The rash gradually faded and had disappeared by 1.5.44. The temperature returned to normal on 30.4.44. The urine was normal throughout the reaction. Desensitisation was commenced on 2.5.44 with 0.01mg. of mapharside. It was completed and treatment continued without further reaction. A summary of treatment is given below:-

21.4.44.	0.45g. neoarsphenamine.	0.2g. bismuth oxychloride.
24.4.44.	0.6g. neoarsphenamine.	0.2g. bismuth oxychloride.
29.4.44.	9th day erythema.	0.2g. bismuth oxychloride.
2.5.44.	0.01g. mapharside.	
3.5.44.	0.02g. mapharside.	
4.5.44.	0.04g. mapharside.	0.2g. bismuth oxychloride.
6.5.44.	0.06g. mapharside.	
10.5.44.	0.06g. mapharside.	0.2g. bismuth oxychloride.
13.5.44.	0.06g. mapharside.	

Subsequently mapharside was given twice weekly without further reaction.

Case No. 3.

Male aged 31 years. Diagnosis: Secondary syphilis.

This patient gave a history of gonorrhoea eight months before admission to hospital. He was a case of secondary syphilis with mucous lesions on the anterior surface of the scrotum, an injected but not ulcerated throat, a psoriasiform rash with generalised adenitis and a healed chancre on the glans penis. Dark-ground examination of serum from a mucous lesion revealed Treponema pallidum and the Wassermann Reaction was reported as strongly positive.

Treatment was started on 18.10.44 when he was given 0.06g. of mapharside and 0.2g. bismuth oxychloride. A further 0.06g. of mapharside was given on the following day as this patient had been placed on an intensive course of mapharside. No treatment was given on the following day but 0.06g. mapharside was given on each of the two subsequent days.

On 24.10.44 the patient complained of headache and malaise. His temperature rose to 101 deg.F. There was slight nuchal rigidity and a macular rash over the trunk and limbs. The rash was most marked over the dorsum of the feet and the pyrexia continued for three days, varying between 99 deg.F. and 101.8 deg.F. By the fourth day the temperature had returned to normal and the rash was fading. During the acute stage of this reaction there was vomiting and slight diarrhoea. The white blood count on 26.10.44, the second day of the reaction, was as follows:-

White blood count: 5,300 per c.mm.

Differential white blood count:

Polymorphonuclear neutrophils	65%
Eosinophils	1%
Basophils	2%
Large lymphocytes ...	7%
Small lymphocytes ...	24%
Large mononuclears ...	2%

This count was repeated on 29.10.44 with the following result:-

White blood count: 6,300 per c.mm.

Differential white blood count:

Polymorphonuclear neutrophils	51%
Eosinophils	10%
Basophils	2%
Large lymphocytes ...	5%
Small lymphocytes ...	29%
Large mononuclears ...	3%

On 28.10.44. desensitisation was commenced and followed by intensive treatment without further reaction. A total of 1.5g. of mapharside was given. A summary of treatment is given below:-

18.10.44. 0.06g. mapharside. 0.2g. bismuth oxychloride.

19.10.44. 0.6g. mapharside.

21.10.44. 0.6g. mapharside.

22.10.44. 0.6g. mapharside.

24.10.44. Erythema of the 9th day. 0.2g. bismuth oxychloride.

27.10.44. Rash fading. Temperature normal 0.2g.bi.oxychlor.

28.10.44. 0.001g. mapharside.

29.10.44.	0.002g.	mapharside.	
30.10.44.	0.004g.	mapharside.	
31.10.44.	0.01g.	mapharside.	0.2g. bismuth oxychloride.
1.11.44.	0.02g.	mapharside.	
2.11.44.	0.04g.	mapharside.	
3.11.44.	0.06g.	mapharside.	
5.11.44.	0.06g.	mapharside.	0.2g. bismuth oxychloride.
6.11.44.	0.06g.	mapharside.	
7.11.44.	0.06g.	mapharside.	
9.11.44.	0.06g.	mapharside.	0.2g. bismuth oxychloride.

Treatment was continued until a total of 1.5g. of mapharside had been given without further reaction.

Case No. 4.

Male aged 29 years. Diagnosis: Primary syphilis.

This patient was admitted to hospital on 22.11.43 and diagnosed as sero-negative primary syphilis. He received 0.45g. neoarsphenamine and 0.2g. bismuth oxychloride on the day of admission. On 25.11.43 he was given 0.6g. neoarsphenamine and 0.2g. bismuth oxychloride. This was repeated on 29.11.43.

On 1.12.43 he presented a maculo-erythematous rash on the trunk and limbs and complained of general malaise, sore throat, generalised aching and pains in all his large joints. His temperature rose to 100.4 deg.F. but returned to normal in 48 hours The white blood count was performed on 2.12.43.

White blood count: 4,800 per c.mm.

Differential white blood count:

Polymorphonuclear neutrophils	62%
Eosinophils	6%
Basophils	0%
Large lymphocytes ...	6%
Small lymphocytes ...	25%
Large mononuclears ...	0%
Transitional cells ...	1%

By 5.12.43 the rash had faded except for the macules which, on the dorsum of the feet and insteps had become petechial. There was no enlargement of the superficial lymphatic glands. All that remained of the rash on 10.12.43 was a few fading petechiae. On 11.12.43 desensitisation was commenced.

Following desensitisation, mapharside was given in twice weekly doses of 0.06g. without further reaction. The patient complained of stiffness in the shoulders following the first two desensitising doses.

Treatment was as follows;-

22.11.43.	0.45g. neoarsphenamine.	0.2g. bismuth oxychloride
25.11.43.	0.6g. neoarsphenamine.	0.2g. bismuth oxychloride
29.11.43.	0.6g. neoarsphenamine.	0.2g. bismuth oxychloride
1.12.43.	Erythema of the 9th day.	
6.12.43.		0.2g. bismuth oxychloride
11.12.43.	0.01g. mapharside.	
13.12.43.	0.2g. mapharside.	0.2g. bismuth oxychloride
17.12.43.	0.04g. mapharside.	
20.12.43.	0.04g. mapharside.	0.2g. bismuth oxychloride
27.12.43.	0.04g. mapharside.	0.2g. bismuth oxychloride
3.1.44.	0.06g. mapharside.	0.2g. bismuth oxychloride
9.1.44.	0.06g. mapharside.	0.2g. bismuth oxychloride

Treatment was continued with 0.06g. mapharside twice weekly without further reaction.

Case No. 5.

Male aged 29 years. Diagnosis: Secondary syphilis.

This man was admitted on 22.3.44 with secondary syphilis. He exhibited peri-anal condylomata lata and marked ulceration of the soft palate and tonsils. Dark-ground examination of serum from the condylomata lata showed Treponema pallidum and the Wassermann Reaction was reported to be strongly positive. Treatment was commenced on 22.3.44 with 0.45g. neoarsphenamine and 0.2g. bismuth oxychloride. On 25.3.44 he was given 0.6g. neoarsphenamine and 0.2g. bismuth oxychloride. This was repeated on the morning of 30.3.44.

During the evening of 30.3.44 his temperature rose to 100.2 deg.F. and an erythematous rash appeared on his fore-arms and thighs. This was accompanied by malaise and headache but no other symptoms. The pyrexia subsided in three days and the rash faded completely in six days.

White blood count: 8,600.

Differential white blood count:

Polymorphonuclear neutrophils	53%
Eosinophils	4%
Basophils	1%
Large lymphocytes ...	5%
Small lymphocytes ...	35%
Large mononuclears ...	2%

Desensitisation was commenced on 14.4.44 with 0.001g. mapharside and followed by therapeutic doses of mapharside without further reaction.

A summary of treatment is given below:-

22.3.44.	0.45g. neoarsphenamine.	0.2g. bismuth oxychloride.
25.3.44.	0.6g. neoarsphenamine.	0.2g. bismuth oxychloride.
30.3.44.	0.6g. neoarsphenamine.	0.2g. bismuth oxychloride.
	Erythema of the 9th day.	
5.4.44.		0.2g. bismuth oxychloride.
9.4.44.		0.2g. bismuth oxychloride.
14.4.44.	0.001g. mapharside.	
15.4.44.	0.002g. mapharside.	
16.4.44.	0.005g. mapharside.	0.2g. bismuth oxychloride.
17.4.44.	0.01g. mapharside.	
18.4.44.	0.02g. mapharside.	
22.4.44.	0.04g. mapharside.	0.2g. bismuth oxychloride.
26.4.44.	0.06g. mapharside.	

Treatment was continued with weekly injections of 0.06g. mapharside without further reaction.

Case No. 6.

Male aged 28 years. Diagnosis: Primary syphilis.

This patient was admitted on 27.5.44 with sero-negative primary syphilis and commenced treatment on that day with 0.45g. neoarsphenamine and 0.2g. bismuth oxychloride. On 30.5.44 he was given 0.6g. neoarsphenamine and 0.2g. bismuth oxychloride. This was repeated on 4.6.44 and 10.6.44. He exhibited no reaction until the 15th day of treatment following the fourth injection of neoarsphenamine when he complained of headache, malaise, and a sore throat with aching gums. He had a generalised adenitis but no fever and an erythematous rash on the backs of the hands and the dorsum of the feet which appeared to be swollen, but did not pit on pressure. His symptoms disappeared in four days without treatment. Three weeks later arsenic was resumed with 0.6g. of a different brand of neoarsphenamine; exactly the same symptoms recurred. A white blood count performed at this time was as follows:-

White blood count: 5,400.

Differential white blood count:

Polymorphonuclear neutrophils	55%
Eosinophils	14%
Basophils	1%
Large lymphocytes ...	10%
Small lymphocytes ...	15%
Large mononuclears ...	5%

Two months later the reaction occurred again after an

injection of 0.45g. of a third brand of neoarsphenamine. One month later on 23.9.44 desensitisation was commenced with 0.001g. mapharside. Following desensitisation therapeutic doses of mapharside were administered without reaction.

A summary of the treatment given is detailed below:-

27.5.44.	0.45g. neoarsphenamine.	0.2g. bismuth oxychloride
30.5.44.	0.6g. neoarsphenamine.	0.2g. bismuth oxychloride
4.6.44.	0.6g. neoarsphenamine.	0.2g. bismuth oxychloride.
10.6.44.	0.6g. neoarsphenamine.	0.2g. bismuth oxychloride.
	Erythema of the 9th day.	
17.6.44.		0.2g. bismuth oxychloride.
24.6.44.		0.2g. bismuth oxychloride.
1.7.44.	0.6g. neoarsphenamine.	0.2g. bismuth oxychloride.
	Recurrence of erythema.	
7.7.44.		0.2g. bismuth oxychloride.
15.7.44.		0.2g. bismuth oxychloride.
22.7.44.		0.2g. bismuth oxychloride.
26.8.44.	0.45g. neoarsphenamine.	0.2g. bismuth oxychloride.
	Recurrence of erythema.	
2.9.44.		0.2g. bismuth oxychloride.
9.9.44.		0.2g. bismuth oxychloride.
16.9.44.		0.2g. bismuth oxychloride.
23.9.44.	0.001g. mapharside.	0.2g. bismuth oxychloride.
30.9.44.	0.002g. mapharside.	0.2g. bismuth oxychloride.
7.10.44.	0.004g. mapharside.	0.2g. bismuth oxychloride.
16.10.44.	0.004g. mapharside.	0.2g. bismuth oxychloride.
23.10.44.	0.01g. mapharside.	0.2g. bismuth oxychloride.
6.11.44.	0.02g. mapharside.	

14.11.44. 0.04g. mapharside.

20.11.44. 0.06g. mapharside.

Treatment was continued with 0.06g. mapharside weekly without further reaction.

Case No. 7.

Male aged 20 years. Diagnosis: Primary syphilis.

This man was admitted to hospital with sero-positive primary syphilis. Treatment was commenced on 20.10.44 when he received 0.45g. neoarsphenamine and 0.2g. bismuth oxychloride. Five days later he complained of malaise and a scarlitiniform rash appeared on the forearms and trunk with vesicle formation on the forearms. The temperature rose to 99,6 deg. F. and the superficial lymphatic glands in the neck and the epitrochlear glands now became palpable, the inguinal and axillary glands having been enlarged before treatment. There was some nuchal rigidity and diarrhoea. A trace of albumen appeared in the urine but this was transient, lasting only 24 hours and no casts were present. The pyrexia lasted for 24 hours only and a differential white blood count revealed no eosinophilia. The rash faded in six days.

Desensitisation was carried out using neoarsphenamine, without further reaction. The initial desensitising dose was 0.01g. A summary of treatment is given below:-

20.10.44.	0.45g. neoarsphenamine.	0.2g. bismuth oxychloride
23.10.44.		0.2g.bismuth oxychloride.
25.10.44.	Erythema of the 9th day.	
27.10.44.		0.2g.bismuth oxychloride.
28.10.44.	0.01g. neoarsphenamine.	
29.10.44.		0.2g.bismuth oxychloride.
30.10.44.	0.02g. neoarsphenamine.	
1.11.44.	0.1g. neoarsphenamine.	
4.11.44.	0.2g. neoarsphenamine.	0.2g.bismuth oxychloride

6.11.44.	0.3g. neoarsphenamine.	0.2g. bismuth oxychloride.
13.11.44.	0.45g. neoarsphenamine.	0.2g. bismuth oxychloride.
20.11.44.	0.6g. neoarsphenamine.	0.2g. bismuth oxychloride.
27.11.44.	0.6g. neoarsphenamine.	0.2g. bismuth oxychloride.

Weekly treatment with 0.6g. neoarsphenamine was continued without the recurrence of intolerance to the drug.

Case No. 8.

Male aged 34 years. Diagnosis: Primary syphilis.

This patient was admitted to hospital on 8.2.44 with seropositive primary syphilis. On the day of admission to hospital he received 0.45g. neoarsphenamine and 0.2g. bismuth oxychloride. On 11.2.44. he was given 0.6g. neoarsphenamine and 0.2g. bismuth oxychloride.

On 15.2.44. he complained of mild headache and a sore throat, and the temperature was 99.2 deg.F. There was a generalised enlargement of the superficial lymphatic glands, a maculo-erythematous rash on the arms and trunk and nuchal rigidity. The urine was normal. Examination of a blood film revealed no increase in the eosinophil white cells. On the following day the rash became vesicular on the forearms and spread to the lower limbs. Subsequently it faded and disappeared in six days.

Desensitisation was carried out and treatment was completed without further reaction. A summary of treatment is given below-

8.2.44.	0.45g. neoarsphenamine.	0.2g. bismuth oxychloride.
11.2.44.	0.6g. neoarsphenamine.	0.2g. bismuth oxychloride.
15.2.44.	Erythema of the 9th day.	
22.2.44.	0.1g. neoarsphenamine.	0.2g. bismuth oxychloride.
25.2.44.	0.2g. neoarsphenamine.	
28.4.44.	0.4g. neoarsphenamine.	0.2g. bismuth oxychloride.
3.3.44.	0.6g. neoarsphenamine.	

Treatment was subsequently completed without further reaction.

Case No. 9.

Male aged 23 years. Diagnosis: Primary syphilis.

This case was admitted to hospital with sero-negative primary syphilis on 6.8.44. He commenced treatment on that day with 0.45g. neoarsphenamine and 0.2g. bismuth oxychloride. He received two further injections of 0.6g. neoarsphenamine and two of 0.2g. bismuth oxychloride on 9.8.44 and 13.8.44. On 15.8.44 he complained of sore throat, stiffness of the neck and malaise. There was a macular rash on the face, trunk and limbs, nuchal rigidity, enlargement of the superficial lymph glands and the temperature rose to 104.2 deg.F. A differential white blood count showed an eosinophilia of 6%. Two days later he had diarrhoea and vomiting. The rash became purpuric on 19.8.44.

On 26.8.44 desensitisation was commenced with 0.01g. of mapharside. On 28.8.44 he was given 0.02g. of mapharside and this was followed by an erythematous rash of the trunk and limbs which lasted for 24 hours. On 1.9.44 a further attempt at desensitisation beginning with 0.001g. of mapharside was made. This was successful and treatment was concluded without further reaction. A summary of treatment is given below:-

6.8.44.	0.45g. neoarsphenamine.	0.2g. bismuth oxychloride.
9.8.44.	0.6g. neoarsphenamine.	0.2g. bismuth oxychloride.
13.8.44.	0.6g. neoarsphenamine.	0.2g. bismuth oxychloride.
15.8.44.	Erythema of the 9th day.	
21.8.44.		0.2g. bismuth oxychloride.
26.8.44.	0.01g. mapharside.	0.2g. bismuth oxychloride.
28.8.44.	0.02g. mapharside. Recurrence of erythema.	

1.9.44.	0.001g. mapharside.	
2.9.44.	0.002g. mapharside.	0.2g. bismuth oxychloride.
4.9.44.	0.004g. mapharside.	
6.9.44.	0.01g. mapharside.	
8.9.44.	0.02g. mapharside.	0.2g. bismuth oxychloride.
10.9.44.	0.04g. mapharside.	
13.9.44.	0.06g. mapharside.	

Treatment was subsequently continued without further reaction.

To summarise:-

1. Nine cases of the syndrome of erythema of the 9th day are described together with the subsequent treatment given.
2. Five cases (Nos. 1, 3, 5, 6 and 9) were successfully desensitised when the first desensitising dose was 0.001g. mapharside.
3. Two cases (Nos. 2 and 4) were successfully desensitised starting with a dose of 0.01g. mapharside.
4. One case (No. 7) was desensitised commencing with 0.01g. of neoarsphenamine.
5. One case (No. 6) who experienced reactions to three different brands of neoarsphenamine was ultimately desensitised successfully with mapharside, commencing with a dose of 0.001g.
6. One case (No. 9) reacted to an initial desensitising dose of 0.01g. of mapharside. Successful desensitisation was achieved when the initial dose was reduced to 0.001g. of mapharside.

(b) Haemorrhagic Encephalopathy.

Haemorrhagic encephalopathy following the administration of the arsphenamines is a rarity. Moore (15) gives the figures for his own cases as 2 in 45,000 treated patients. Moore and Stokes (5) point out that this complication occurs more commonly in European peoples than in Americans, but note that reports in the American literature are becoming more numerous. Many cases of haemorrhagic encephalopathy have been described recently in the literature. (49, 50, 51, 52, 53 and 54).

The condition often occurs early in the treatment of syphilis usually after the first few injections of a trivalent arsenical compound. It will be noted that this corresponds in time with the occurrence of the syndrome of erythema of the 9th day. The condition usually becomes manifest 48 hours after the last injection of the arsenical compound and is heralded by pyrexia and headache, followed by deepening coma and delirium. Manifestations of the focal lesions in the brain occur, including Jacksonian fits and there may be remissions and exacerbations of these symptoms. Petechiae in the skin may occur and albumen and casts may be found in the urine. In about 75% of cases death occurs. Deep coma, loss of reflexes and hyperpyrexia characterise the terminal picture. The cerebrospinal fluid is under pressure and its protein is increased; frequently there is no increase in the cells. At autopsy, generalised oedema of the brain is found with multiple punctate and ring haemorrhages most commonly seen in the basal ganglia.

Subendocardial haemorrhages may be present.

The recommended treatment includes sedation, lumbar puncture, venesection and adrenaline every four hours, in large doses. Ransome and Paterson recommend that these cases be nursed in the sitting position. (52).

One case of haemorrhagic encephalopathy occurred in this group of toxic reactions and the case report and post-mortem findings were as follows.

Case 1.

Male aged 39 years. Diagnosis: Secondary syphilis.

This patient was admitted to hospital on 9.6.43. He had healed sores on the frenum and glans penis, a maculo-papular rash on the trunk and limbs, generalised enlargement of the superficial lymph glands, early anal condylomata lata and a mucous patch on the right side of the upper lip. There was a patch of varicose eczema on the right leg at the site of an old, healed varicose ulcer. Dark-field examination of serum from the condylomata lata showed Treponema pallidum and the Wassermann Reaction was strongly positive.

On 10.6.43. he received 0.45g. neoarsphenamine and 0.2g. bismuth oxychloride. The following day he complained of headache malaise and pain over the area of varicose eczema on the right leg. The temperature rose to 103.4 Deg.F. A diagnosis of Herxheimer reaction was made and the patient confined to bed. The following day on 12.6.43 the temperature was normal and the patient felt well. On 15.6.43 and on 22.6.43, 0.6g.neoarsphenamine and 0.2g. bismuth oxychloride were given. On 23.6.44

the patient complained of headache and slight nausea but the temperature was normal. These symptoms had improved by 24.6.43. but pain recurred in the patch of varicose eczema. On the evening of 25.6.43 headache recurred. The patient was seen at 07.30 hours on 26.6.43 when he had some clonic contractions of the lower jaw, rolling of the eyes and a bitten tongue. He was unconscious and was considered to be recovering from an epileptiform fit. The temperature was normal. His recovery was anticipated and he was given phenobarbiton gr.1 intramuscularly. Coma and slight clonic contractions of his jaw continued and a diagnosis of acute haemorrhagic encephalopathy was made. The pupils reacted normally to light and the reflexes were present. Adrenaline m10 was given intramuscularly and lumbar puncture performed. The fluid appeared to be under pressure, was clear and colourless and 20cc. were removed. Examination of the fluid revealed an increase in the protein content. Venesection was performed and 90cc. of blood were withdrawn. At 12.00 hours the patient was in a deep coma with stertorous breathing and had become incontinent of urine. The tendon and corneal reflexes were absent, the pupils were moderately dilated and did not react to light. Adrenaline m10. was given intramuscularly. The temperature was 99.8 deg.F. the pulse 120 per minute and the blood pressure 130/80. By 18.00 hours the temperature had risen to 105 deg.F. A further 15cc. of cerebrospinal fluid were removed and 1cc. of adrenaline given. This resulted in a slight improvement of the general condition but was followed by deepening coma and death at 01.40 hours on 27.6.43.

Report of the Post Mortem Examination carried out at 16.00 hours on 18.6.43.

External Appearances.

This man appeared to be of normal height and build and of good nutrition. There was a red area on the under surface of the glans penis just to the right of the frenum about 5 m.m. in diameter with the appearance of a healed chancre. There were old brown scars scattered over the right tibia (about 1 c.m. in diameter) and some loss of external skin over the inner side of the right ankle. Posteriorly there was the mark of a recent lumbar puncture .

Internal Appearances.

Head and Brain.

There were about a dozen petechial patches on the dura mater over the body of the sphenoid, just anterior to the sella turcica There was a diffuse congestion over the surface of both hemispheres which was probably a post mortem phenomenon. There was no evidence of acute meningitis. No lesions of any kind were seen on careful naked-eye examination of the brain.

Neck and thorax.

There was some congestion of the lower half of the trachea with numerous pin point petechiae in the mucosa, and some purplish congestion of the thyroid gland. The colloid content was normal. There was about 5 c.c. of clear fluid in the pericardium. The heart weighed 10 oz. and was very dilated, all chambers being affected. The valves were normal and the

heart muscle cloudy, probably from autolysis. There were a group of subendocardial haemorrhages about the centre of the left surface of the interventricular septum. The left coronary artery was almost but not quite occluded by atheroma about 1½ cm. from its origin. The remainder of this coronary artery and the right coronary artery were normal.

Both lower lobes of the lungs were grossly oedematous and showed early bronchopneumonia with some areas of early softening. The smaller bronchi in this area were filled with yellow pus.

Abdomen.

The liver showed gross autolytic changes with many areas of foaminess. The pancreas, spleen and kidneys also showed autolytic changes. All the other findings in a full post mortem examination were normal.

Conclusions.

The original lesion was the chancre on the glans penis, which was healed. There was no remaining evidence of secondary syphilis. The complete absence of any cerebral lesions evident to the naked eye was surprising in view of the history of encephalopathy following treatment with neoarsphenamine. The subendocardial haemorrhages were in keeping with death from a cerebral condition. The small petechiae in the sphenoidal dura mater were presumably related to the encephalopathy. The coronary atheroma was of serious degree, but did not appear to have played any part in the fatal outcome.

This was a typical example of acute arsenical encephalopathy terminating fatally. The symptoms referred to the site of previous varicose ulceration are of interest and may be of some significance in relation to the other cerebral manifestations of sensitisation. It is of interest to note the signs of vascular degeneration in this case. While no significant conclusion is justified it is difficult not to be impressed by this association of vascular degeneration and a rare vasculo-toxic reaction.

(c) Agranulocytosis.

Although agranulocytosis is the most common example of blood dyscrasia complicating arsenotherapy, it is a rarity. The other blood dyscrasias which occur are purpura and aplastic anaemia. These reactions occur most frequently after the use of sulpharsphenamine. Individual cases may present one or all of these blood dyscrasias and the mortality rate is high. Moore (15) quoting from the publications of McCarthy, Wilson and Loveman gives the following figures:-

Dyscrasia.	No. of cases.	% Mortality Rate.
Haemorrhagic purpura	12	-
Haemorrhagic purpura and agranulocytosis	7	14.2
Agranulocytosis	15	33.3
Aplastic anaemia	36	80.5

Agranulocytosis following the use of neoarsphenamine has been recently reported by various authors (75, 76, 77). The condition usually occurs early in treatment but may occur after many injections of the offending drug have been given.

In agranulocytosis the patient complains of sore throat, aching gums and general malaise with pyrexia. As the condition progresses sloughing, with inflammatory enlargement of the cervical glands, appears on the pharynx and fauces including tonsils. There is diminution or complete absence of the granulocytic elements of the blood and the patient is consequently highly

susceptible to pyogenic infection.

One patient with agranulocytosis following the use of neoarsphenamine was studied and after desensitisation with mapharside his treatment was completed. A brief case report is given below.

Case 1.

Male aged 36. Diagnosis: Secondary syphilis.

This patient was admitted to hospital on 2.5.44 suffering from secondary syphilis having been exposed to infection about nine weeks previously. He had multiple chancres on the glans penis and prepuce, generalised adenitis, a maculo-roseolar rash on the trunk and mucous lesions in his mouth. Dark-ground examination of serum from the penile lesions showed Treponema pallidum and the Wassermann Reaction was strongly positive. Anti-syphilitic treatment with neoarsphenamine and bismuth oxychloride was commenced and between 2.5.44 and 7.6.44 he received 3.95g. of neoarsphenamine and 1.4g. of bismuth oxychloride. On 14.6.44 when he reported for treatment he complained of a sore throat and general malaise. He appeared to have an acute tonsillitis with injection of the fauces and had a temperature of 99.8 deg.F. He was admitted to my wards and given potassium chlorate gargles and aspirin gr.10 four hourly. The urine was normal. On the following day the temperature rose to 104 deg.F. he looked ill and a greyish slough was present on the left tonsil 34,000 units of anti-diphtheritic serum were given, a throat swab was taken and he was given sulphathiazole 4g. daily. On 16.6.44 the temperature had fallen to 99.2 deg.F. and the

membrane had spread to both tonsils, the anterior pillars of the fauces and along the gums behind the last two molar teeth. A blood count was performed.

Red blood corpuscles: 4,200,000.

Haemoglobin (Haldane): 86%

White blood count: 6,500.

No granular cells were seen when a film of the blood was examined.

20cc. pentnucleotide were given intramuscularly and again eight hours later. The following day on 17.6.44 a further 40cc. of pentnucleotide were given in two doses of 20cc. The white blood count was 5,500 per c.mm. and the blood film contained 5% myelocytes. On 18.6.44 a blood film contained 10% polymorphonuclear neutrophils and 6% myelocytes. The general condition of the patient appeared to be better and no further treatment was given. During the next two days the granular cells in the blood rose to 40% and the local condition in the mouth improved greatly. An uninterrupted convalescence followed.

On 21.8.44 approximately one month after the occurrence of agranulocytosis, desensitisation using mapharside was carried out a close check being maintained on the blood picture. Mapharside was continued subsequently in twice weekly doses of 0.06g.until a total of 1.8g. had been given without further reaction.

A summary of treatment is given below:-

2.5.44 to 7.6.44.	4.05g. neoarsphenamine.	1.4g. bismuth oxychloride
14.6.44.	Agranulocytosis.	

12.7.44 to 1.8.44.		0.8g. bismuth oxychloride.
2.8.44.	0.001g. mapharside.	0.2g. bismuth oxychloride.
4.8.44.	0.002g. mapharside.	
5.8.44.	0.004g. mapharside.	0.2g. bismuth oxychloride.
7.8.44.	0.01g. mapharside.	
9.8.44.	0.02g. mapharside.	0.2g. bismuth oxychloride.
12.8.44.	0.04g. mapharside.	
16.8.44.	0.04g. mapharside.	0.2g. bismuth oxychloride.
19.8.44.	0.04g. mapharside.	
22.8.44.	0.06g. mapharside.	0.2g. bismuth oxychloride.

Treatment was continued with 0.06g. mapharside twice weekly, without further reaction.

During the period of this study no example of aplastic anaemia or arsenical purpura occurred.

Park (46) has shown that agranulocytosis following sulphonamide therapy is a sensitisation reaction and has successfully achieved desensitisation. Falconer Epstein and Mills(68) have shown that agranulocytopaenic purpura following the use of neoarsphenamine is also a sensitisation phenomenon. From the above mentioned reports and the case herewith recorded it is concluded that agranulocytosis following arsenotherapy is a sensitisation phenomenon and that desensitisation of such cases can be successfully effected.

(d) Arsenical Dermatitis (excluding Exfoliative Dermatitis).

Moore (15) gives the following table of incidence of the major post-arsphenamine skin reactions. The material is from that collected by the Co-operative Clinical Group.

Drug.	No. of injections.	Incidence of Dermatitis per 1,000 injections.
Arsphenamine	105,942	0.90
Neoarsphenamine	30,779	0.81
Tryparsamide	19,964	0.15
Bimarsen	8,552	0.23
Sulpharsphenamine	7,912	1.39
Silverarsphenamine	3,848	0.52
Mapharsen	56,290	0.053

In the present study of arsenical dermatitis this reaction was observed in 10 cases out of a group receiving 12,000 injections of neoarsphenamine. This gives a rate of 0.83 per 1,000 injections which is almost identical with the above quoted analysis.

Various theories of the cause of post-arsphenamine dermatitis have been postulated. It has been shown however, that many years after this complication has occurred, even minute doses of an arsphenamine will cause a recurrence of the dermatitis (15). This phenomenon can only be explained on a basis of allergy.

As has already been stated, exfoliative dermatitis has been dealt with separately. The dermatological reactions which did not go on to exfoliation have been divided into two groups according to their presumed aetiology. The first group consists

of the cases which exhibited a pure allergic reaction to neoarsphenamine and the second group is composed of individuals of the seborrhoeic type who had an exacerbation or initial attack of seborrhoeic dermatitis during their treatment with neoarsphenamine.

In the latter group six cases were investigated, three of whom had been treated for seborrhoeic dermatitis prior to receiving neoarsphenamine. The remaining three experienced their initial attack during their antisyphilitic treatment. In all these cases desensitisation was unsuccessful in spite of the use of mapharside and different proprietary brands of neoarsphenamine. In these cases, after a short rest and treatment of the seborrhoeic dermatitis, arsenic was tolerated for a few injections but in all cases sooner or later the dermatitis recurred. It is considered that the insertion of these case records would serve no useful function but for the sake of completeness the record of a typical case is given.

Case report.

Male aged 24 years. Diagnosis: Primary syphilis.

This patient was admitted to hospital with sero-positive primary syphilis on 30.4.43.

Treatment was commenced on 30.4.43. and the first course of treatment was completed without reaction although he had had an attack of seborrhoeic dermatitis two years previously. During the rest period following the first course of treatment he had a mild seborrhoeic dermatitis of the back of the neck.

This cleared up when treated with Lassar's paste and the second course was commenced on 17.7.43. On 27.8.43. after the fifth injection of this course, he complained of an itchy rash on the back of the neck and on the arms. On examination, this proved to be a recurrence of the seborrhoeic dermatitis. Neoarsphenamine was stopped and Lassar's paste applied locally. He had some seborrhoea of the scalp. This was treated with 2% sulphur and 2% salicylic acid in a water soluble base. The injections of bismuth oxychloride were continued.

On 20.3.44, the patient's skin being in a satisfactory condition, 0.1g. neoarsphenamine was given. This resulted in a mild recurrence of the reaction and treatment was continued for three weeks with bismuth only. On 31.3.44, 0.001g. mapharside was given without reaction. Attempted desensitisation was continued and by 14.4.44 the patient was receiving 0.06g. mapharside. Weekly injections of 0.06g. were tolerated for five weeks, when there was a recurrence of the dermatitis. Treatment was continued with bismuth only.

Two months later desensitisation with mapharside was again attempted and mapharside was given in therapeutic doses for five weeks after which the dermatitis recurred and treatment thereafter was with bismuth only.

Seven cases in which the aetiology was considered to be a sensitisation reaction to neoarsphenamine alone were studied and desensitisation was attempted and carried out successfully in six of these. The case records are given below.

Case No. 1.

Male aged 29 years. Diagnosis: Primary syphilis.

This patient was admitted to hospital suffering from sero-positive primary syphilis and treatment was commenced on 7.9.43 with 0.45g. neoarsphenamine and 0.2g. bismuth oxychloride. After five injections of neoarsphenamine a mild erythematous rash developed on the upper limbs on 15.10.43. This subsided without treatment after arsenic was discontinued. On 13.12.43, 0.04g. mapharside was given without reaction and on 20.12.43, 0.06g. mapharside was given. This resulted in an acute itchy papulo-vesicular rash on both arms and legs, principally on the flexor surfaces. This was treated with calamine lotion and Lassar's paste and subsided completely in three weeks.

On 24.3.44, three months later, desensitisation was commenced with mapharside 0.001g. and adequate treatment was eventually completed without further reaction.

A summary of treatment is as follows:-

7.9.43.	0.45g. neoarsphenamine.	0.2g. bismuth oxychloride.
11.9.43.	0.6g. neoarsphenamine.	0.2g. bismuth oxychloride.
18.9.43.	0.6g. neoarsphenamine.	0.2g. bismuth oxychloride.
24.9.43.	0.6g. neoarsphenamine.	0.2g. bismuth oxychloride.
1.10.43.	0.6g. neoarsphenamine.	0.2g. bismuth oxychloride.
8.10.43.	0.6g. neoarsphenamine.	0.2g. bismuth oxychloride
15.10.43.	Dermatitis.	0.2g. bismuth oxychloride.
26.10.43.		0.2g. bismuth oxychloride.
30.11.43		0.2g. bismuth oxychloride.

6.12.43.		0.2g. bismuth oxychloride.
13.12.43.	0.04g. Mapharside.	0.2g. bismuth oxychloride.
20.12.43.	0.06g. Mapharside.	0.2g. bismuth oxychloride.
21.12.43.	Recurrence of dermatitis.	
27.12.43 to 25.2.44.		2.0g. bismuth oxychloride.
24.3.44.	0.001g. Mapharside.	0.2g. bismuth oxychloride.
31.3.44.	0.01g. Mapharside.	0.2g. bismuth oxychloride.
7.4.44.	0.02g. Mapharside.	0.2g. bismuth oxychloride.
14.4.44.	0.04g. Mapharside.	0.2g. bismuth oxychloride.
21.4.44.	0.06g. Mapharside.	0.2g. bismuth oxychloride.
28.4.44.	0.06g. Mapharside.	0.2g. bismuth oxychloride.

Treatment was continued without further reaction.

Case No. 2.

Male aged 39 years. Diagnosis: Secondary syphilis.

When first seen this patient presented florid secondary syphilis with healed sores on the penis and scrotum, a wide-spread papulo-squamous rash, generalised adenitis, condylomata lata around the anus and mucous lesions in the mouth. Treatment was started on 28.4.44 and the first course of ten injections was completed without reaction by 24.6.44. After five injections of the second course, he complained of a slightly itchy papular rash on the legs and forearms. The administration of arsenic was stopped and the rash faded in three weeks. On 23.9.44 he was given 0.3g. of a different brand of neoarsphenamine. This resulted in an acute recurrence of the dermatitis with an itchy papulo-erythematous rash on the arms, forearms, face and legs. The rash subsided in three weeks with local treatment. On 21.10.44 desensitisation using mapharside was commenced and treatment was subsequently completed without further reaction.

A summary of treatment is given below:-

28.4.44 to 24.6.44.	5.85g. neoarsphenamine and	2.0g. bismuth oxychloride.
22.7.44.	0.45g. neoarsphenamine.	0.2g. bismuth oxychloride.
29.7.44.	0.6g. neoarsphenamine.	0.2g. bismuth oxychloride.
5.8.44.	0.6g. neoarsphenamine.	0.2g. bismuth oxychloride.
12.8.44.	0.6g. neoarsphenamine.	0.2g. bismuth oxychloride.
19.8.44.	0.6g. neoarsphenamine.	0.2g. bismuth oxychloride.
	Dermatitis.	
26.8.44.		0.2g. bismuth oxychloride

2.9.44.		0.2g. bismuth oxychloride.
9.9.44.		0.2g. bismuth oxychloride.
16.9.44.		0.2g. bismuth oxychloride.
23.9.44.	0.3g. neoarsphenamine.	
	Recurrence of dermatitis.	
21.10.44.	0.001g. mapharside.	0.2g. bismuth oxychloride.
28.10.44.	0.002g. mapharside.	0.2g. bismuth oxychloride.
4.11.44.	0.004g. mapharside.	0.2g. bismuth oxychloride.
13.11.44.	0.01g. mapharside.	0.2g. bismuth oxychloride.
18.11.44.	0.02g. mapharside.	0.2g. bismuth oxychloride.
25.11.44.	0.04g. mapharside.	0.2g. bismuth oxychloride.
1.12.44.	0.06g. mapharside.	0.2g. bismuth oxychloride.

Treatment was continued with mapharside without further reaction.

Case No. 3.

Male aged 25 years. Diagnosis: Primary syphilis.

This patient was admitted to hospital with sero-positive primary syphilis. He commenced treatment for his infection on 16.1.44 and exhibited no reaction to treatment until after the 21st injection of neoarsphenamine on 10.7.44. On 16.7.44 he developed a maculo-vesicular rash with an erythematous background on both forearms. He complained of itching over the area of the rash. Calamine lotion was applied locally and the rash subsided and disappeared in eight days. On 7.8.44 desensitisation with 0.001g. of mapharside was commenced and during and after desensitisation no further reaction to arsenic was experienced.

A summary of treatment is given below:-

16.1.44 to 13.3.44.	5.85g. neoarsphenamine.	2.0g. bismuth oxychloride.
10.4.44 to 12.6.44.	5.85g. neoarsphenamine.	2.0g. bismuth oxychloride.
10.7.44.	0.45g. neoarsphenamine.	0.2g. bismuth oxychloride.
16.7.44.	Dermatitis.	
17.7.44.		0.2g. bismuth oxychloride.
24.7.44.		0.2g. bismuth oxychloride.
31.7.44.		0.2g. bismuth oxychloride.
7.8.44.	0.001g. mapharside.	0.2g. bismuth oxychloride.
14.8.44.	0.002g. mapharside.	0.2g. bismuth oxychloride.
21.8.44.	0.004g. mapharside.	0.2g. bismuth oxychloride.
28.8.44.	0.01g. mapharside.	0.2g. bismuth oxychloride.
4.9.44.	0.02g. mapharside.	0.2g. bismuth oxychloride.
11.9.44.	0.04g. mapharside.	0.2g. bismuth oxychloride.

18.9.44.	0.04g.	mapharside.	0.2g. bismuth oxychloride.
25.9.44.	0.6g.	mapharside.	
2.10.44.	0.6g.	mapharside.	

Treatment with 0.06g. mapharside was continued without further reaction.

Case No. 4.

Male aged 23 years. Diagnosis: Congenital syphilis.

This patient was admitted to hospital on 15.1.44 with balanitis and was diagnosed as congenital syphilis because of a repeatedly strongly positive Wassermann Reaction and the presence of stigmata. He commenced treatment for syphilis on 26.1.44 with bismuth only and did not receive any injections of neoarsphenamine until 15.3.44, when he was given an initial dose of 0.3g. of neoarsphenamine.

On 24.7.44 after 15 injections of neoarsphenamine he complained of an itchy rash on his arms. On examination there was a vesiculo-erythematous rash on both forearms, principally affecting the ante-cubital fossae and flexor surfaces of the forearms. Calamine lotion was applied locally and the injections of neoarsphenamine were discontinued. The rash disappeared in eleven days.

On 21.8.44 just less than one month after this reaction, desensitisation was commenced using 0.001g. of mapharside. Desensitisation and treatment were completed without further reaction.

A summary of treatment is given below:-

26.1.44 to 8.3.44.		1.2g. bismuth oxychloride.
15.3.44 to 19.5.44.	4.2g. neoarsphenamine.	1.8g. bismuth oxychloride.
26.6.44.	0.45g. neoarsphenamine.	0.2g. bismuth oxychloride.
3.7.44.	0.45g. neoarsphenamine.	0.2g. bismuth oxychloride.

10.7.44.	0.45g. neoarsphenamine.	0.2g. bismuth oxychloride.
17.7.44.	0.45g. neoarsphenamine.	0.2g. bismuth oxychloride.
24.7.44.	Dermatitis.	0.2g. bismuth oxychloride.
31.7.44.		0.2g. bismuth oxychloride.
7.8.44.		0.2g. bismuth oxychloride.
14.8.44.		0.2g. bismuth oxychloride.
21.8.44.	0.001g. mapharside.	0.2g. bismuth oxychloride.
28.8.44.	0.002g. mapharside.	0.2g. bismuth oxychloride.
4.9.44.	0.005g. mapharside.	0.2g. bismuth oxychloride.
11.9.44.	0.01g. mapharside.	
18.9.44.	0.2g. mapharside.	
25.9.44.	0.4g. mapharside.	
2.10.44.	0.06g. mapharside.	

Treatment was concluded using mapharside without further reaction.

Case No. 5.

Male aged 36 years. Diagnosis: Secondary syphilis.

This patient was admitted with secondary syphilis. He had no evidence of a primary lesion but had a pustular syphilide of the forearms and a faint generalised maculo-roseolar rash on the trunk. There was a generalised adenitis, healing mucous lesions in the mouth and condylomata lata around the anus. Treatment was commenced on 19.10.43, the first ten injections of neoarsphenamine being completed by 15.12,43 without any reaction.

On 18.2.44 after a further six injections of neoarsphenamine he developed a typical, itchy, papulo-vesicular rash on the arms and behind the knees. Arsenic was stopped and the rash involuted in 18 days with local treatment with calamine lotion.

On 2.5.44 desensitisation with mapharside was commenced and followed with therapeutic doses of mapharside without further reaction.

The treatment was as follows:-

19.10.43 to 15.12.43.	5.55g. neoarsphenamine.	0.2g. bismuth oxychloride
13.1.44.	0.45g. neoarsphenamine.	0.2g.bismuth oxychloride.
20.1.44.	0.6g. neoarsphenamine.	0.2g.bismuth oxychloride
27.1.44.	0.6g. neoarsphenamine.	0.2g.bismuth oxychloride
3.2.44.	0.6g. neoarsphenamine.	0.2g.bismuth oxychloride
10.2.44.	0.6g. neoarsphenamine.	0.2g.bismuth oxychloride
17.2.44.	0.6g. neoarsphenamine.	0.2g.bismuth oxychloride
18.2.44.	Dermatitis.	
24.2.44.		0.2g.bismuth oxychloride

3.3.44.		0.2g. bismuth oxychloride.
10.3.44.		0.2g. bismuth oxychloride.
17.3.44.		0.2g. bismuth oxychloride.
21.4.44.		0.2g. bismuth oxychloride.
2.5.44.	0.001g. mapharside.	0.2g. bismuth oxychloride.
9.5.44.	0.002g. mapharside.	0.2g. bismuth oxychloride.
16.5.44.	0.004g. mapharside.	0.2g. bismuth oxychloride.
23.5.44.	0.01g. mapharside.	0.2g. bismuth oxychloride.
30.5.44.	0.02g. mapharside.	0.2g. bismuth oxychloride.
6.6.44.	0.04g. mapharside.	0.2g. bismuth oxychloride.
13.6.44.	0.06g. mapharside.	0.2g. bismuth oxychloride.

Treatment was continued with mapharside without further reaction.

Case No. 6.

Male aged 42 years. Diagnosis: Syphilis (muco-cutaneous relapse)

This patient had a muco-cutaneous relapse eighteen months after inadequate therapy, and was admitted to hospital for further treatment. He had previously received four injections of arsenic and four of bismuth. He completed two full courses of neoarsphenamine and bismuth and twenty days after the last injection of the second course (20th injection) on 29.6.43, he complained of pain in his shoulders, knees and ankles. An itchy maculo-papular rash was present over the knees and ankles together with a few macules in both ante-cubital fossae. Jaundice occurred on 17.7.43. Treatment was continued with bismuth only.

On 1.12.43. desensitisation was commenced with 0.001g. mapharside and following this adequate treatment was completed without further reaction.

A summary of treatment is given below:-

8.1.43 to 10.3.43.	5.55g. neoarsphenamine.	2.0g. bismuth oxychloride.
7.4.43 to 9.6.43.	5.85g. neoarsphenamine.	2.0g. bismuth oxychloride.
29.6.43.	Pain in joints and dermatitis.	
17.7.43.	Jaundice.	
17.7.43 to 26.10.43.	2.4g. bismuth oxychloride.	
.1.12.43.	0.001g. mapharside.	0.2g. bismuth oxychloride.
5.12.43.	0.002g. mapharside.	0.2g. bismuth oxychloride.
12.12.43.	0.004g. mapharside.	0.2g. bismuth oxychloride.
17.12.43.	0.01g. mapharside.	0.2g. bismuth oxychloride.

24.12.43.	0.02g. mapharside.	0.2g. bismuth oxychloride.
31.12.43.	0.04g. mapharside.	0.2g. bismuth oxychloride.
7.1.44.	0.06g. mapharside.	0.2g. bismuth oxychloride.

Treatment was continued and subsequently completed without further reaction.

Case No. 7 has been included here, being one of interest, although desensitisation was not carried out.

Case No. 7.

Male aged 24 years. Diagnosis: Secondary syphilis.

Secondary syphilis was diagnosed on 16.12.42 and he developed a papulo-erythematous rash on the flexor surfaces of the arms and legs on 1.3.43 after one course (10 injections) of neoarsphenamine. On 10.3.43 he developed jaundice. Treatment was continued with bismuth only.

One year later on 8.3.44. neoarsphenamine was resumed in therapeutic doses without any attempt at desensitisation. No reaction resulted. The first dose given was 0.3g.neoarsphenamine the second 0.45g. neoarsphenamine and subsequent doses were 0.6g.

To summarise:-

1. 7 cases with cutaneous reactions to neoarsphenamine of a seborrhoeic type could not be desensitised with trivalent arsenical drugs.
2. 6 cases with cutaneous reactions to neoarsphenamine were desensitised using mapharside and commencing with an initial dose of 0.001g. In all these cases adequate treatment was subsequently completed without further intolerance.
3. In one case neoarsphenamine was resumed in therapeutic doses one year after a cutaneous reaction without the occurrence of further signs of intolerance.

(g) Exfoliative Dermatitis.

Exfoliative dermatitis following the use of the arsphenamines is a complication which may endanger life. As Stokes (5) has stated: "This complication it will be recalled, ranks second only to haemorrhagic encephalitis as the most fatal of all unavoidable complications of a properly conducted arsphenamine therapy". Moore (15) gives the incidence per 1,000 injections as ranging from 1,39 with sulpharsphenamine to 0.053 with mapharsen. He considers that exfoliative dermatitis is a sensitisation reaction and emphasises that subsequently, even a minute dose of a trivalent arsenical compound will provoke a generalised dermatitis. This statement implies that the reaction is allergic rather than toxic.

A new approach to the elucidation of this sensitisation phenomenon has resulted from a study of cellular metabolism. Peters (55) has pointed out that the carbohydrates, glucose and glycogen, are broken down in the cells to carbon dioxide and water, each step being controlled by a definite enzyme and may involve phosphorylations. One of the later products of the process is pyruvic acid and the pyruvate oxidase system contains a component sensitive to very small quantities of arsenic. It follows that the metabolism of carbohydrate is poisoned at an important stage by traces of an arsenical. British anti-lewisite (synonyms. B.A.L. and Ox. 217) ($CH_2SH.CHSH.CH_2OH$) is a simple 1,2 dithiole and is capable of exerting a marked antidotal action against the poisoning of the pyruvate oxidase system by trivalent arsenicals and of reversing this poisoning when once

established. These effects are brought about by the ability of the 1,2 dithiole to form stable ring compounds with the trivalent arsenicals. B.A.L. was made up in a 5% W/V solution in 10% W/V benzyl benzoate in pea-nut oil and was administered intramuscularly. It was considered that B.A.L. administered to a case of exfoliative dermatitis might shorten the duration of the attack and reduce its severity. Two cases of exfoliative dermatitis following the administration of neoarsphenamine were treated with B.A.L.; a third received symptomatic treatment only. Desensitisation was not attempted because of the known hypersensitivity of these cases and the potential danger to life. Brief clinical records of the cases with notes on their treatment are appended.

Case No. 1.

Male aged 25 years. Diagnosis: Secondary syphilis.

This patient was admitted to hospital on 7.10.43 with a maculo-papular rash, a small penile sore and a generalised enlargement of the superficial lymphatic glands. Dark-ground examination revealed Treponema pallidum and the Wassermann Reaction was positive.

Treatment was commenced on 8.10.43 and between this date and 7.12.43 he received 5.0g. neoarsphenamine and 2.4g. bismuth oxychloride. He experienced no prodromal symptoms of dermatitis during this period.

On 23.12.43 he was re-admitted to hospital with exfoliative dermatitis of six days duration. On examination there was a generalised exfoliative dermatitis affecting the whole of the dermis. The skin at the flexures was cracked and there were cracks behind both ears. The scalp was scaling and there was a folliculitis of the back and shoulders, blepharitis, conjunctivitis and a small abscess at the outer canthus of the left eye. There was no pyrexia.

Treatment with calamine in oil to the skin and boric irrigations to the eyes was instituted.

On 26.12.43 the temperature was 99.0 deg.F. and the general condition was satisfactory. There was no change in the skin. On 30.12.43 the abscess at the outer canthus of the left eye was incised and the cracks behind the ears had become grossly infected The condition of the skin improved during the next few days but the folliculitis on the back and shoulders became more marked

and furuncles developed on the pubic region. On 7.1.44 the condition of the skin was improved and there was much desquamation in all areas. On 9.1.44, 10.1.44 and 11.1.44 the patient received 2cc. B.A.L. intramuscularly twice daily, a total of 12cc. in all.

By 14.1.44 the skin was greatly improved, although desquamation was still proceeding, but multiple abscesses of the neck, shoulders, pubic area, chest and limbs had developed. These were treated by incision and dressed with 12.5% sodium sulphate compresses. On 18.1.44 the skin was free of all scaling except for the scalp and the soles of the feet. The texture of the skin was very good, being smooth and elastic. The superficial abscesses increased in number and the residual sepsis lasted for a further two months.

Case No. 2.

Male aged 47 years. Diagnosis: Primary syphilis.

This patient was admitted to hospital on 9.11.43 suffering from sero-negative primary syphilis. Between 10.11.43 and 5.1.44 he received 5.85g. neoarsphenamine and 2g. bismuth oxychloride. On 12.11.43 he complained of an itchy rash on his wrists, forearms and thighs. A diagnosis of scabies was made and he was treated with benzyl benzoate. Between 3.2.44 and 24.2.44 he received 2.25g. neoarsphenamine and 0.8g. bismuth oxychloride without any reaction. On 25.2.44 he developed an itchy papulo-erythematous rash on both forearms. This was treated with calamine lotion but did not improve and on 14.3.44 he was re-admitted to hospital with exfoliative dermatitis. On admission there was marked scaling of the scalp and a generalised dusky pink erythematous rash with early exfoliation and weeping of the flexures. The hands and feet were not involved at this time. The temperature was 100.4 deg.F. Calamine cream was applied to the skin and 2% sulphur and 2% salicylic acid in soft paraffin applied to the scalp. On the following day the temperature had fallen to 98.6 deg.F. The patient complained of sore throat and numbness of the hands. The skin remained unchanged but the fauces were injected and there was slight oedema of the dorsum of the hands. A differential white blood count showed an eosinophilia of 25.3% By 16.3.44 the condition of the scalp had improved and there was less scaling present but furuncles were developing in both axillae and on the pubic region. There were also infected cracks behind both pinnae.

On the following day, exfoliation had become generalised except for the hands and feet, and the patient's temperature was 99 deg. F. On 18.3.44 treatment with B.A.L. was initiated and injections of 2 cc. were given intramuscularly twice daily for the next five days until a total of 24 cc. had been given. During this period abscesses developed in both axillae and the desquamation proceeded. Desquamation of the hands and feet did not occur until 28.3.44. On 30.3.44 the general condition was satisfactory and the sepsis in the axillae had almost resolved. On 12.4.44 there was slight scaling of the scalp and flexures although the remainder of the skin was satisfactory. The skin at the flexures did not return to normal for many months.

Case No. 3.

Male aged 29 years. Diagnosis: Primary syphilis.

This patient was admitted to hospital on 6.4.44 suffering from sero-negative primary syphilis. Between 6.4.44 and 1.6.44 he received 5.85g. neoarsphenamine and 2.0g. bismuth oxychloride. Between 30.6.44 and 6.7.44 he received 1.05g. neoarsphenamine and 0.4g. bismuth oxychloride. He was re-admitted to hospital on 13.7.44 with dermatitis. On admission the temperature was 99.8 deg. F. and the patient had a raised erythematous rash on the arms, legs, face and scalp with some oedema of the face. Calamine lotion was applied locally. The pyrexia continued and the condition of the skin deteriorated. On 15.7.44 all areas of the skin were affected and there were weeping cracks at the flexures and behind the left pinna. The hair from the scalp, axillae and pubic area was shaved off and Lassar's paste applied to all areas. Three days later there was exfoliation of the scalp, face and limbs with large weeping areas on the neck, flexures and lower abdomen. On 20.7.44 there was some improvement of the skin and exfoliation continued, while two furuncles had developed on the pubic area. Exfoliation of the hands and feet commenced on 26.7.44. By this time the weeping areas were improving and the furuncles on the pubic area were discharging. Improvement continued steadily and by 15.8.44 exfoliation had ceased, but there were still small weeping areas at the flexures. The skin had healed completed by 26.8.44.

To summarise:-

1. Three cases of exfoliative dermatitis are described. One case treated with B.A.L. showed marked improvement in the texture of the skin and in a second case treated similarly the results were inconclusive.
2. Secondary infection of the skin is a common and serious complication of exfoliative dermatitis. It is considered that the onset of this complication may be encouraged by the use of greasy or oily topical applications and a limited experience suggests that dry applications after shaving of the glabrous skin may be beneficial.

DISCUSSION.

The management of the reactions to the trivalent arsenical drugs in this group has been conducted on the hypothesis that all these reactions are allergic in nature. In 1927 Frei (61) first demonstrated that arsphenamine dermatitis was the result of sensitivity rather than a direct toxic action. Falconer, Epstein and Mills (68) have shown that purpura following the use of a trivalent arsenical preparation is an allergic reaction. Cases No. 5 and 6 of erythema of the 9th day and Cases No. 1 and 2 of post-arsphenamine dermatitis in Section II, confirm the hypothesis.

The work of Landsteiner and Jacobs (62) suggests that arsphenamine unites with a homologous serum or tissue protein to form a hapten antigen. It is probable that the formation of antigen is intradermal in origin. Shaffer (78) first suggested that minute doses of arsenic might be deposited in the skin as the needle was being withdrawn after the intravenous injection of the arsphenamines. Cormia (59) and others have reported the occurrence of postarsphenamine dermatitis following accidental, peri-venous injection of neoarsphenamine and it is generally accepted that the intra-dermal route offers the greatest prospects of success in experimental sensitisation.

It is considered that the trivalent arsenical drugs probably combine with a tissue or serum protein to form an antigen which stimulates the formation of antibody and that when the antigen and homologous antibody combine in sufficient quantity the sensitisation reactions become manifest. This may be

expressed crudely in the formula given below, the reaction obeying the mass law.

A. (antigen) + B. (antibody) ⟶ C. (products of the reaction)

It is only when the production and quantity of C. rises above a threshold level that the state of sensitisation becomes manifest. It is considered that C. is probably excreted slowly. Using this formula as a working hypothesis the process of desensitisation and the phenomena encountered can be explained satisfactorily.

The process of desensitisation consists in adding a hapten antigen (A.) to combine with antibody (B.) at such a rate as to maintain the production of the products of the reaction (C.) below the threshold level required for the production of sensitisation reactions. Thus should the initial dose of A. cause a reaction by raising the production of C. above the threshold level, a smaller dose should be given subsequently. This is illustrated after erythema of the 9th day by Case No.9, and Cases 2, 4 and 7 demonstrate that if the amount of antibody produced by a particular individual is small, larger doses of A. may be given with impunity. Cases 1 and 2 of post-arsphenamine dermatitis demonstrate that neoarsphenamine and mapharside have homologous specificity and when given intravenously act as haptens.

Cases of seborrhoeic dermatitis could not be desensitised and because of the potential danger to life no attempt was made to confirm the fact that this is also applicable to exfoliative dermatitis. Sulzberger and Rostenburg (79) have demonstrated the correctness of polyvalent sensitisation as applied to the

skin. It is probable that in seborrhoeic dermatitis and exfoliative dermatitis further trivalent arsenicals act as a complete antigens and not as haptens, increasing the formation of antibody and making desensitisation impossible.

It is probable that antibody is slowly excreted. This would account for the fact that in case No. 7 of arsenical dermatitis, the administration of neoarsphenamine one year after the occurrence of dermatitis was not followed by further signs of intolerance.

This group of reactions is found after the use of several drugs, particularly those containing a benzene ring, and desensitisation as described above would probably be applicable in all cases.

CONCLUSIONS.

It may be concluded that:-

1. Following the administration of neoarsphenamine, erythema of the 9th day, agranulocytosis and arsenical dermatitis are allergic reactions.
2. Following erythema of the 9th day, agranulocytosis and dermatitis, short of exfoliation, due to neoarsphenamine, desensitisation can be carried out and further therapeutic doses of a trivalent arsenical given.
3. Desensitisation cannot be carried out in cases of dermatitis following neoarsphenamine where the reaction is of a seborrhoeic nature.
4. No definite conclusion concerning the use of B.A.L. in exfoliative dermatitis can be reached but it is considered that further investigation may show that the preparation has a place in the treatment of this reaction to arsenotherapy.

SUMMARY.

Introduction.

1. The objects of the study are given.
2. The material is described and the methods used in case taking, examination and in laboratory procedures are given in detail.

Section I.

1. A clinical study and analysis of the signs and symptoms of primary and secondary syphilis in a series of 250 cases is described and photographs illustrating cases are included.
2. It is concluded that syphilis as studied in this series of cases is a less virulent disease than that described as occurring in the 19th Century.

Section II.

1. A study of the reversal of the serological reactions of the blood in relation to treatment, with various schedules of trivalent arsenical compounds and with penicillin, in 979 cases of primary or secondary syphilis is described.
2. It is concluded that:-
   (a) Neoarsphenamine should be administered regularly, twice weekly, in adequate dosage to obtain satisfactory serological reversal.
   (b) Satisfactory results in the reversal of the serological reaction of the blood in cases of primary and secondary syphilis can be achieved with mapharside.
   (c) A total dosage of 2,400,000 Oxford Units of penicillin is not adequate treatment for all cases of primary and

secondary syphilis. Further consideration of the optimum dosage and of the "time/dosage" factor in such cases, is required.

Section III.

1. A study of the major reactions to the trivalent arsenical compounds and an investigation into new methods of management of these reactions is described.

   (a) An injection technique for the prevention of post-arsphenamine jaundice is described, the use of which reduced the incidence of the reaction from 42% to less than 1%. The aetiology of post-arsphenamine jaundice is discussed.

   (b) Nine cases of erythema of the 9th day are described with their management by a process of desensitisation.

   (c) One fatal case of haemorrhagic encephalopathy is described and the results of the post-mortem examination are given.

   (d) One case of agranulocytosis following the administration of neoarsphenamine is described with subsequent arsenotherapy after desensitisation.

   (e) A typical case of seborrhoeic dermatitis aggravated by the administration of the trivalent arsenical compounds is described with unsuccessful attempts at desensitisation.

   (f) Seven cases of dermatitis of an allergic type following the administration of neoarsphenamine are described with

successful desensitisation using mapharside.

(g) Three cases of generalised exfoliative dermatitis following the administration of neoarsphenamine, two of which were treated with B.A.L., are described.

2. It is concluded that:-

(a) "Post-arsphenamine jaundice" is usually an infective hepatitis, indistinguishable from epidemic infective hepatitis and its spread amongst patients receiving arseno-therapy can be prevented.

(b) Following the administration of the trivalent arsenical drugs, erythema of the 9th day, agranulocytosis and certain types of dermatitis are allergic phenomena and following desensitisation arsenotherapy can be continued. The principles used can probably be applied to the whole group of drugs which cause these reactions.

(c) Desensitisation cannot be carried out in seborrhoeic individuals exhibiting dermatitis during treatment with the trivalent arsenical drugs.

(d) No definite conclusion concerning the use of B.A.L. in the management of exfoliative dermatitis due to arsenic could be reached.

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