FURTHER PROGRESS IN VENEREOLOGY*

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ANTIBIOTICS

(a) **Penicillin.**—Most significant developments have taken place in the field of antibiotics, especially with repository penicillins. The treatment, which used to consist of injections every 2 to 4 hours with aqueous penicillins, daily with penicillin in oil-beeswax, and sometimes once or twice weekly with procaine penicillin with aluminium monostearate, may now be achieved by a single or a few injections.

Two new long-acting penicillins are :

(i) N.N'-dibenzylethylene diamine dipenicillin G (Benzathine penicillin G) ; after a single injection of 600,000 units detectable serum levels may be obtained for 2 weeks or more.⁶

(ii) Benethamine penicillin (N-benzyl-β-phenylethylamine penicillin G), which gives a less prolonged level than the former.

One of these two compounds or their derivatives may one day prove to be the penicillin for general use in venereology, but at present they are both locally more painful than P.A.M., and P.A.M. thus remains the preparation of choice.^{10a}

Another experimental product is "Benemid", a new preparation with a caronamide action.^{5 25}

Other new penicillins are :

(i) Penicillin G diethylaminoethylester hydriodide ("Neopenil"), which has produced cerebrospinal fluid levels ten times as high as other penicillins,²⁰

(ii) P 92—a penicillin salt of N-methyl-1:2 diphenyl 2-hydroxythelamine—which is supposed to give a low incidence of reactions,¹³

(iii) Allylmercaptomethyl penicillin (penicillin O) which is stated to be able to be used in persons allergic to benzyl penicillin,¹ although some observers²² consider that skin sensitivity tests should first be made.

Trials have been undertaken with Benzathine, a mixture containing 300,000 units potassium penicillin G, 300,000 units procaine penicillin G, and 600,000 units penicillin in a 2-ml. dose. A high initial penicillin serum level, a moderately high intermediate level, and a prolonged low level for 15 days or more were noted in the majority of subjects tested.¹⁷

Considering the vast quantities of penicillin now being used, its freedom from toxic effects is remarkable.

Occasional reactions have from time to time been reported and these have been considered in general.^{15 21} In a study of one hundred syphilitics treated with procaine penicillin with aluminium monostearate, an increased cutaneous response to the stroking of a pin was noted in 80 per cent. and an eosinophilia in all of 22 tested.¹¹ Reactions to procaine penicillin in the form of feelings of impending death have been reported in eight patients,⁴ and a fatal case of cerebral purpura in a congenital syphilitic treated with penicillin has been recorded,¹⁹ as have also cases of anaphylactic shock some of which were fatal,^{14 23 24} and serum sickness-like reactions.¹⁶ How penicillin-sensitive persons may be desensitized has also been described.²

It was found that a number of P.A.M. preparations on the commercial market were not up to standard as regards duration of serum levels. An investigation sponsored by the World Health Organization resulted in definite specifications being formulated for repository penicillins to be used in W.H.O. programmes—the most important one being that a penicillin serum level of 0.03 units or above should be obtained for 72 hrs or more in the majority of subjects after an intramuscular injection of 300,000 units.⁸ It was also suggested that the vastus lateralis is the best site for intramuscular injections.³

(b) **Other Antibiotics.**—Allergic reactions with streptomycin have again been reported.²¹ The toxic effects of the orally administered antibiotics have been described previously.²⁸

A number of new antibiotics have been used. Magnamycin, prepared from *Streptomyces halstedii*, is effective in granuloma inguinale but ineffective in lymphogranuloma venereum and gonorrhoea.²⁷ Erythromycin (Ilotycin), prepared from *Streptomyces erythreus*, is effective in gonorrhoea⁷ and granuloma inguinale,¹⁸ and possesses an antisiphilic action.¹² The bacterial spectra of erythromycin, carbomycin, chloramphenicol, aureomycin, and terramycin have also been compared.²⁸ Preliminary studies have also been made in Japan of Trichomycin, an antibiotic prepared from *Streptomyces hachijoensis*, which has some action on *T. vaginalis* and fungi,⁹ and also on *T. pallidum*.¹⁰

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GONORRHOEA

(a) **General.**—That gonorrhoea in the female is often asymptomatic and may lurk in the para-urethral glands has again been emphasized.³⁴ Rectal infection was noted in 31 per cent. of 142 cases of urogenital gonorrhoea; 45 of these persons were questioned and 24 admitted anal coitus.²⁵

Four cases of primary gonococcal infection of the

skin,²⁰ one case of fixed eruption of the penis resulting from sulphonamides given in the treatment of the disease,⁹ one of erythema nodosum in association with gonorrhoea,⁴¹ one of gonococcal parotitis,¹⁵ one of gonococcal meningitis,¹⁷ and one of gonococcal pericarditis with effusion,¹⁰ have been reported, as has one fatal case of gonococcal myocarditis²⁶ and one case of death from heart failure following a dose of mixed gonococcal vaccine.²¹ The incidence of the gonococcus in cases of Bartholinitis has also been considered.⁴

Persons who have repeated attacks of gonorrhoea have been studied,⁶ as have those with repeated infections with both gonorrhoea and syphilis.²⁹ In investigations concerning the routes of infection in marital partners it was noted that gonorrhoea travelled more often than syphilis from male to female, while in syphilis the reverse was the case. Extramarital relationships in females were found to be more steady than in males and therefore more conducive to the spread of syphilis than to that of gonorrhoea.²⁷

Urethral biopsy specimens taken from patients with gonorrhoea have been examined⁴³ and the oxidation of amino acids by the gonococcus has been considered,⁴⁴ as have media suitable for the culture of the gonococcus during transit.^{30 37} No advantage has been found in adding thallium acetate to the media.² The use of enzymatic casein hydrolysates in media has also been discussed.⁴²

(b) **Treatment.**—The modern management of gonorrhoea has been reviewed^{31 46 47} and a campaign against gonorrhoea in a district of Greenland has been described.⁴⁰ Although possible variations in the penicillin sensitivity of the gonococcus have been reported,^{38 39} penicillin remains the drug of choice. In a series of 192 patients given a single injection of 900,000 units of a repository penicillin no failures were noted.⁷ Penicillin is sometimes given orally²⁴ but injection methods are preferred. Some authors have used sulphonamides in addition,^{22 32} but these are considered to be unnecessary.

No further series treated with streptomycin are reported although a case with a streptomycin-resistant gonococcus has been recorded.³⁶ Chloramphenicol has been used by a number of workers:^{3 7 12 35} of 103 cases given a single oral dose of 3 g. there were no failures,⁷ while of 226 patients given a single oral dose of 2 g., 93.3 per cent. were satisfactory a week later.³ Of 51 patients given a single 1-g. intramuscular injection, 86 per cent. were cured.³⁵ Trials have also been undertaken with a mixture of chloramphenicol, sulphathiazole, and an antihistaminic ('Sinactin') which, probably erroneously, was claimed not to mask syphilis.¹ Aureomycin achieved 94.3 per cent. of cures in 122 patients given 1 g. orally, but the same cure rate was noted with half this dose combined with 0.668 g. of each of three sulphonamides.⁵² Terramycin has also been used.^{48 49 50} In 202 cases given 2 g. there was a cumulative relapse rate at 22 to 28 days of 10.7 per cent. as compared with 7.7 per cent. after 150,000 units procaine penicillin.⁵¹

Erythromycin has also been shown to be effective. Of thirty patients given 2 g. orally in single or divided doses,

96.6 per cent. were cured, but with 1 g. only 50 per cent.¹⁹ Mild side-reactions, including nausea, vomiting, cramps, and drowsiness, were noted in seven patients. Magnamycin, however, proved ineffective. In doses of 0.5 to 2 g. given intravenously or orally, there were 38 failures in 41 patients treated.⁴⁵

A 2 to 4 per cent. solution of tripeleminamine hydrochloride (an antihistamine drug) has been used as a local anaesthetic for urethral manipulation.¹⁶ Cortisone has been given to 31 patients with urethral stricture in an attempt to delay the fibroblastic response following dilatation, with encouraging results in seventeen.⁸ The operation of cornual resection has been employed in the treatment of 114 cases of gonococcal salpingitis.¹⁴

OCULAR GONORRHOEA.—An epidemic of gonococcal conjunctivitis in Algeria has been reported.²⁹ Of 6,442 persons legally declared blind in Ohio, U.S.A., over a 10-year period, in 68 the blindness was due to gonococcal ophthalmia.¹⁸ In the prophylaxis of ophthalmia neonatorum, penicillin ointment has been used as an alternative to silver nitrate;^{5 13 28} incidence of non-specific conjunctivitis was 11 per cent. with silver nitrate and 2.5 per cent. with penicillin.⁵ Penicillin combined with sulphonamides,³³ and sulphonamide preparations alone,¹¹ have also been used.

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GRANULOMA INGUINALE

Granuloma inguinale has been considered in French Guiana,³ in India,⁸ in Java,²⁰ and in Northern Australia,²¹ and a case has also been reported in a woman who had never been out of Scotland.² Freak cases include an infant infected during birth,¹⁹ and one with pulmonary infiltration, splenomegaly, and liver biopsy appearances resembling sarcoid.¹¹ The association of granuloma inguinale with carcinoma has also been considered.^{1 12 16}

The latest methods of diagnosis and treatment have been reviewed,⁶ as have factors necessary for the growth of *Donovania granulomatis*⁴ and complement-fixation tests.⁵

The antibiotics streptomycin,⁷ aureomycin,^{7 9 15} chloramphenicol given orally^{7 13 15} or intramuscularly,^{10 14 18} and terramycin,⁷ continue to give satisfactory results ;

4 g. daily for 5 to 10 days is considered to be a suitable course for streptomycin and 2 g. daily for 10 to 20 days for the others.⁷ Erythromycin¹⁷ and magnamycin²² are apparently also effective.

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LYMPHOGRANULOMA VENEREUM

(a) **General.**—Apart from general considerations of the disease^{15 21 23} and its treatment,^{14 22} and of its vulvar lesions,⁹ a number of papers have been concerned with rectal lymphogranuloma venereum and its complication of stricture.^{2 18 31} Cases of inguinal bubo simulating strangulated hernia have been reported²⁵ as have buboes in the neck.^{24 27} How much certain ocular signs which have been described have to do with the disease has yet to be decided.³³ A depression of pallesthesia has been noted in lymphogranuloma venereum which usually becomes normal within a year of the cessation of therapy.⁶

There are conflicting reports as to whether the disease may predispose to cancer. Although positive skin tests

have been reported in 26 per cent. of patients with carcinoma of the penis and 15 per cent. with carcinoma of the vulva,²⁰ and cases of concomitant disease have been recorded,³⁰ statistical evidence does not indicate any such association.³⁰ The opinion has been advanced that the causative organism lies on the border line between protozoa and fungi, possibly belonging to the mycetozoa, or slime-moulds.¹⁹

The use of the Frei test has indicated that asymptomatic persons may constitute an infectious reservoir of the disease.⁸ Positive readings were obtained in 32.7 per cent. of prostitutes in Brazil.²⁸ A positive Frei test may be temporarily suppressed by cortisone⁷ and the intensity of the reaction often bears no relationship to the titre of the complement fixation test.⁸ In the latter test prozone phenomena occasionally cause difficulties.²⁶

(b) **Treatment.**—The newer antibiotics aureomycin,^{3 4 5 13} chloramphenicol given orally,³ or intramuscularly,¹⁷ and terramycin^{3 11} have given good results in early cases. In late cases with stricture of the rectum the results have been less striking³ and other measures may be required.¹⁶ Magnamycin is ineffective.²⁹ The sulphonamides continue to give fair results³² and slow but steady improvement may even be brought about by the use of vaccine lymph.¹⁰ A new preparation 2 : 3 dimethyl quinoxaline has been tested against the virus¹² and tried in seventeen cases.¹ Results were fairly good or better in only nine and skin complications and/or muscle cramps occurred in twelve. It thus proved inferior to the antibiotics.

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NON-SPECIFIC URETHRITIS

(a) **General.**—In 1952 there were 11,552 new cases of non-specific urethritis in the clinics of England and Wales as compared with 15,510 new male cases of gonorrhoea.²⁷ The disease has been prevalent amongst U.S. forces in the Far East^{3 13 14} and amongst U.S. servicemen returning from overseas.⁹ Non-specific urethritis is now receiving the attention it deserves in the United States but not everywhere is it yet entirely accepted as a venereal disease.^{2 6}

Several workers have considered its aetiology.^{4 19} The disease has a longer incubation period than gonorrhoea and is apparently more likely to affect married men than single and white-collar workers than labourers.³⁷ In Great Britain at any rate there is no suggestion that buccal or anal coitus is responsible for the bulk of cases.³⁷

(b) **Aetiology.**—Routine cultures from urethra and prostate provide little evidence to support a diagnosis of bacterial urethritis.² The claim of pleuropneumonia-like organisms (P.P.L.O.) to be the cause has also been considerably weakened. "L" organisms have been considered,¹⁶ their protein growth factor studied,³² and their reduction by tetrazolium salts investigated,³³ as have human and genital strains of P.P.L.O.¹¹ These have been isolated from men with non-specific urethritis^{22 28 29} and from women with leucorrhoea.^{22 29} However, P.P.L.O. have been found also in persons with no genital abnormality²⁸ and do not seem to be related either to the disease^{28 36} or to other organisms cultured.³⁶ They have also been reported in a patient with fusospirillary vulvovaginitis.³⁰ Moreover they have been found to be highly resistant to erythromycin¹⁸ although personal studies indicate that this antibiotic may be effective in non-specific urethritis.

Viral urethritis has also been considered,^{5 7 8} although confirmation of a virus causation for the majority of

cases is likewise lacking. Complement-fixation tests for lymphogranuloma venereum showed no tendency to positivity in cases of non-specific urethritis or in their consorts nor did complement-fixation tests for enzootic abortion in ewes, a veterinary disease caused by a virus of the same group, although there was close agreement in the results of the two tests.²⁵ No phase-contrast or electron-microscope studies have been reported, although the virtue of inclusion blennorrhoea has been so examined.³⁵ A case of herpetic urethritis has been described.¹²

Two more observers have reported trichomonads in the discharges of males with non-specific urethritis, in 5.8 per cent.²⁰ and in 10 per cent.³⁴ of cases respectively. Trichomonads have been found in the semen of seven of 26 men whose wives had trichomonad vaginitis,³¹ in five of forty cases of balanitis, and asymptotically in the urethra in one of forty married men, but not in the preputial sacs of sixty promiscuous persons.²⁰ Interesting inoculation experiments have recently been performed. Five male volunteers were inoculated intra-urethrally with cultures of *T. vaginalis*, and all developed a urethritis, trichomonads being demonstrated in three, while nothing was noted in five controls.²¹

Two possible causative organisms have recently been described. One, closely related to the genus *Haemophilus*, is a Gram-negative, non-motile, non-encapsulated pleomorphic rod 0.5 μ wide and 0.5 to 2.0 μ long with a tendency to form haemolytic colonies,²³ and the other a coccobacillary organism.²

Several cases of abacterial cystitis often associated with or following an attack of non-specific urethritis have been reported.^{10 17}

(c) **Treatment.**—Following its first trials in non-specific urethritis,⁴¹ terramycin has been found to be the most satisfactory antibiotic.^{2 15 38 38} In one series a cure rate of 85 per cent. was obtained¹⁵ and in another a cure rate of 80.6 per cent. provided that 5 to 6 g. was given³⁸; 2 g. daily for five days is considered to be the most satisfactory course.

When trichomonads are present,²⁶ good,^{9 15 38} indifferent,¹⁴ and variable results have been reported with aureomycin. Somewhat poorer results have been obtained with chloramphenicol.^{15 38}

Good results have been claimed with sulphonamides in high dosage.¹⁴ Penicillin is not efficient¹⁴ and a cumulative failure rate of 53.3 per cent. has been reported.³⁹ On the other hand, a cure rate of 85.4 per cent. was claimed with a schedule consisting of 1 g. streptomycin plus sulphathiazole 1.5 g. four times daily for 5 days.²⁴

Terramycin, streptomycin, and penicillin,⁴⁰ and likewise sulphathiazole,¹ have not proved successful in aborting non-gonococcal urethritis following the treatment of gonorrhoea.

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REITER'S SYNDROME

Cases of this condition continue to be reported,^{1 2 3 5 6 11 12 13} and its relationship to gonorrhoea has been discussed.¹⁴ A clinical and histological study of balanitis circinata has been made,¹² and 21 cases of arthritis complicating urethritis have been considered in detail.⁴ The complaint was characterized by self-limiting attacks of varying duration which were unaffected by treatment but could be suppressed by cortisone. The series included four cases of ankylosing spondylitis which condition has no association with gonorrhoea.¹⁶

A number of authors have reported on the use of cortisone or A.C.T.H. in Reiter's syndrome.^{4 6 7 10} These hormones are capable of suppressing the disease, and, if their use is continued until the end of a self-limiting attack, an apparent cure is obtained.

The orally administered antibiotics frequently give disappointing results, although aureomycin,¹⁵ chloramphenicol,¹⁷ and terramycin¹⁸ have been stated to be effective in individual cases. Anti-histamine drugs have also been reported to be of value.⁸

It has been noted that in rats orally administered cystein hydrochloride will inhibit arthritis due to pleuropneumonia-like organisms.⁹

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OTHER CONDITIONS

Cat-Scratch Disease.—In this condition regional buboes follow the scratch of an infected cat.^{3 5 15 22 23} If the lower limb is involved these may be mistaken for those due to chancroid or to lymphogranuloma venereum.

Condylomata Acuminata.—Genital warts¹⁸ and their treatment with podophyllin¹³ have been considered. Two cases with giant warts have been described.¹¹ That vulvar warts may predispose to malignancy in the Negro has also been postulated; of eleven cases of carcinoma of the vulva four arose in pre-existing warts.⁴

Trichomoniasis (For trichomoniasis in the male see *Non-Specific Urethritis*).—A review of the literature concerning trichomoniasis has been presented.⁶ In an obstetrical clinic an infestation rate of 20 per cent. has been reported.²⁰ The lavatory seat has again been incriminated as the main source of infection in females.¹⁷ Urinary involvement has been reported in 26·7 per cent. of cases.¹⁹

It has now been claimed to be possible to produce fatal experimental infections with *T. vaginalis* in mice.¹⁴ A simple staining method employing methyl violet has been described.⁹ Trichomonads may apparently survive in association with Döderlein's bacillus and species of syringospores in an acid environment.⁸

Local treatments continue to give rather unsatisfactory results although the value of keeping the vagina dry has been emphasized.¹⁶ Using "Arsenamide", failure rates of 15 to 40 per cent. have been noted.²⁰ A case of dermatitis resulting from the use of acetarsol pessaries has been put on record.⁷ Other substances tried include "Vagisol",²¹ "Tetranyl" by insufflation,¹ "Floroquin" suppositories,¹ and allantomide vaginal cream with aminoacridine.¹

Terramycin pessaries have been reported as giving good results in 21 cases¹² but insufflation with aureomycin powder was used in thirty cases with results similar to those obtained by other methods.¹⁹ Aureomycin inserts used on fifty patients had good results in 29 only.² Experiments with pessaries containing starch suggested that vaginal jellies may remain in the vagina for at least 3 days.²⁵

Behcet's Syndrome.—Cases from the literature totalling 32 and one additional case have been reviewed.¹⁰ Progressive loss of vision was the rule.

Sporotrichosis.—A rare case of affection of the genitalia, showing as localized painless granulomata, has been reported.²⁴

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SOFT SORE

Soft sore generally has been considered³ as has its vulvar lesions.⁵ The disease has been a considerable problem in Korea² and amongst the U.S. forces in Japan, where there were 4,813 cases in 1951 as compared with 147 of syphilis.⁴ Organisms resembling *H. ducreyi* have been found in a high proportion of Japanese prostitutes.¹ Skin tests for chancroid have been reported on 1,022 Africans and significantly higher positivity rates were found in the towns than in the rural areas.¹⁰

In experimental human infections, sulphathiazole, streptomycin, aureomycin, chloramphenicol, and penicillin in high dosage (but not neoarsphenamine, bismuth, or antimony) were found to be effective.¹¹ Streptomycin was used successfully in the clinical infection^{2 8} in doses of 1 g. daily for 5 days, and intramuscular chloramphenicol has also been effective⁶ as has aureomycin.⁷ As they do not mask syphilis the sulphonamides are often preferred.⁹

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SYPHILIS

EXPERIMENTAL SYPHILIS

Immunity.—Immunological studies on *T. pallidum* and *B. anserina* have been reported.²³ No appreciable differences in the anti-spirochaetal activity of plasma and the serum of patients with early syphilis have been noted.²⁶ That some acquired immunity is developed in rabbits against heterologous strains of *T. pallidum* has been observed,^{16 28} although in cured rabbits there was no increase of immunity produced by successive infections.¹⁷ Moreover, mice injected with heat-killed *T. pallidum* developed no active immunity although reagin and treponemal antibody were formed.¹⁷ Comparative immunological studies of the treponematoses have also been undertaken.²⁷

The life-span of mice with asymptomatic syphilis has been shown to be shorter than that of controls.²² In rabbits spirochaetes have been found in small numbers even 3 to 4 years after the disease has become asymptomatic.⁵ Partly immune rabbits treated with penicillin developed local lesions when inoculated intracutaneously with *T. pallidum*, but lymph node involvement was much delayed: lymph node transfer is thus an unreliable method of proof of infection in such animals.²⁹

Renewed attempts have been made to evolve protective inoculation in animals, using a preparation of syphilitic rabbit testicle.^{12 25} Agglutination titres could apparently be made to rise, but no positive Wassermann reactions were induced.

Drugs.—Attempts to produce a penicillin-fast treponeme by giving subcutaneous injections of penicillin have failed.²⁰ It has been noted that with subtreponemastatic levels of penicillin the Nichols and Reiter strains of cultivable treponemes underwent elongation, whereas *T. pallidum* disappeared from syphilitic lesions without changes in morphology.¹⁹ When subcurative doses of penicillin were given during the incubation period the regular logarithmic increment of multiplying treponemes was interrupted and the process reverted to an earlier phase.⁷

Experiments have been undertaken to gauge the effects of penicillin at the site of injection on streptococcal infections in mice. The duration of the penicillin level rather than its height was the most important factor.²

Likewise the most effective penicillin schedule was one in which an effective concentration was continuously maintained.³ No Herxheimer reaction was noted in one series of 25 rabbits treated with penicillin.²¹

In rabbit syphilis both mercury succinimide and potassium iodide have shown a synergistic effect when given with procaine penicillin G,¹⁰ as have bismuth and penicillin,¹⁴ and arsenic, bismuth, and penicillin.⁹ A combination of penicillin and streptomycin has also been studied.²⁴

Terramycin has proved effective in rabbit syphilis,^{1 13} and the effects of bismuth and terramycin have been investigated.¹⁵ The Kazan, Nichols, and Reiter strains have been shown to be highly susceptible to erythromycin.⁸

The activity of arsenoxide with one of a series of antibiotics has been studied. The activity of arsenoxide was enhanced by combining treatment with penicillin, streptomycin, bacitracin, and myocrysin. In contrast interference occurred between arsenoxide and terramycin, aureomycin, and chloramphenicol. It was considered that this therapeutic interference resulted from competition in the fixation-penetration of the organisms.⁴ The effects of hyaluronidase on the treponemacidal action of salvarsan have also been investigated.¹¹ It has been reported that A.C.T.H. does not upset the Herxheimer reaction produced by penicillin.⁶

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EARLY SYPHILIS

General.—Reviews of the literature concerning syphilis^{1 2} have been published, and the age and sex distributions of early syphilis have been discussed.²³

The risk of contracting syphilis from regular intercourse with a syphilitic partner has been considered.²² It has been noted that relatively stable sexual relations are more favourable to the spread of syphilis than to that of gonorrhoea.¹⁵ Transfusion syphilis has been described by a number of authors,^{4 9 11 12 13} as has accidental syphilis as a whole.²⁴ Other matters considered include the diagnosis of syphilis during surveillance of contacts,¹⁷ syphilitic balanitis,¹⁶ syphilitic hepatitis,¹⁹ early gastric syphilis,²¹ and interdigital syphilitic lesions on the feet.⁸ Four cases of juxta-articular nodes in untreated syphilis,²⁰ an apparent case of syphilis combined with infectious mononucleosis,²⁵ and a case of syphilitic nephrosis treated with penicillin⁷ have been reported.

It was noted that 40 per cent. of patients with early syphilis had an accentuated aortic second sound and an aortic systolic murmur recorded by the stethogram.⁵ Abnormalities in the electrocardiogram have been reported in eleven of 29 patients with secondary syphilis,⁶ and the effects of penicillin on the electrocardiogram have also been considered.¹⁴

Destructive osteitis in early syphilis has been described,¹⁸ and radiological studies in early syphilis have been reported.³ A depression of pallesthesia all over the body in early syphilis has been noted, which increased in a Herxheimer-like manner immediately after the first injection of penicillin but which will apparently return to normal after 1 to 2 years.¹⁰

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Treatment.—The present-day management of syphilis has been summarized^{16 31} and modern treatments evaluated.^{1 30} Their effect on syphilis control has been considered.²⁹

Penicillin is now firmly established as the drug of choice in the treatment of early syphilis and further reports from its converts continue to appear.^{6 7 18 34} Only one paper records the use of metallotherapy (bismuth) alone.⁸ The repository penicillins given once a day have yielded as good results as multiple injections of aqueous penicillin,⁵ and the results with procaine penicillin with aluminium monostearate have been, if anything, better than those with penicillin in oil-beeswax.¹⁹ It is apparent that little benefit is obtained by increasing the dosage or the treatment time above 4.8 mega units over 8 days.

Experimentation with single injections of procaine penicillin with aluminium monostearate continues. Data have been presented on 174 patients given single injections of 1.2, 2.4, and 4.8 mega units P.A.M. and followed from 9 months to 5 years. Although 1.2 mega units was considered a satisfactory dose in primary syphilis it was insufficient in secondary syphilis, for which 2.4 mega units was recommended. The re-treatment rate in a series of 124 cases of secondary syphilis given single injections was 13.7 per cent.³³ In another series of sixty patients with secondary syphilis given single injections of 2.4 mega units P.A.M., there was a success rate of 88.2 per cent. after 15 months.²² That many so-called treatment failures are in fact re-infections has again been emphasized.²⁶ A comparison of parenteral and oral methods has been made.²³ It has also been shown that the Herxheimer reaction caused by penicillin is not prevented by 100 mg. cortisone given over 24 hrs.⁶

There has been a marked falling off in the number of papers concerning the treatment of early syphilis

with penicillin in combination with other drugs, and much of the published data refers to the past rather than the present. Penicillin plus mercury schedules have been reported from France,³ penicillin plus arsenic and bismuth schedules from Belgrade,² and also penicillin plus fever.^{12 20 28} The use of orally administered penicillin and fever³⁵ has also been reported; a comparison of penicillin alone with mapharsen plus fever showed no differences in the failure rates.³²

Arsenic is still being used, however, as evidenced by fresh reports of its toxic effects. Fatal cases of arsphenamine poisoning,¹⁴ and of arsenical dermatitis with death from pneumonia⁹ have been recorded, as has a case of arsenical encephalopathy¹⁷ and 76 cases of arsenical erythema.³⁶ In spite of these cases new arsenical preparations are still being tried on the continent of Europe: Spirotrypan^{10 11 27} and Neo-Arsoluin.¹³

Experimental schedules with the orally administered antibiotics have been reported. Aureomycin,^{24 25} chloramphenicol given orally²⁴ and intramuscularly,²¹ and terramycin,^{15 24} have all been used. Occasional cases of resistance have been encountered but the over-all results have been fairly good. It is considered that doses of 2 g. or more should be given daily for 10 to 14 days and that such treatments may be useful for occasional patients who are sensitive to penicillin.

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LATENT SYPHILIS AND LATE BENIGN SYPHILIS

LATENT SYPHILIS

The management of late and latent syphilis^{10 22} and the prognosis of latent syphilis in relation to life insurance⁶ have been discussed, as have the public health aspects of late latent syphilis.⁵ Although the incidence of primary syphilis has fallen markedly since the introduction of penicillin there has been no corresponding fall in the number of cases of late syphilis attending the United States Public Health Service clinics.⁵ In Denmark, on the other hand, in spite of the high incidence of early syphilis during and immediately following World War II, there is now little evidence of any increase in latent syphilis *ignorée*.³⁶

Syphilis and tuberculosis have been discussed,³⁵ as have syphilis and trauma,³⁷ in the consideration of a unilateral psoriasiform syphilide on the hand of a waiter. Other subjects considered include hypopituitarism in male subjects with syphilis³⁰ and the various aspects of fatal syphilis.^{23 28 33}

Pulmonary syphilis has been discussed by a number of authors,^{12 26 27 32} as well as pulmonary syphilitic arteritis,¹ abdominal syphilis,²⁹ gastric syphilis,^{8 13} syphilis of the liver,³⁸ of bone,^{2 4 17} of the muscles,³⁴ of the mouth and teeth,¹⁶ of the mediastinum,²⁰ of the bladder,⁷ and of the female genital organs.¹⁹ The syphilitic dyschromias have also been considered,⁹ and a case of amyloidosis due to syphilis has been described.¹⁸ Other topics covered include syphilis of the eye,²⁵ peculiar ocular manifestations due to syphilis,¹⁴ chronic uveitis which is sometimes syphilitic,³ syphilitic

iridocyclitis,²¹ dacryoadenitis,¹¹ and changes in the fundus with special reference to latent syphilis.³¹

The question of provocation of serum tests in late syphilis by penicillin, mapharsen, and bismuth has also been considered; no evidence of provocation was noted in 12 patients.²⁴ An interesting effect of penicillin has been reported in a case showing gumma and epithelioma of the skin¹⁵; the gumma healed but the epithelioma spread rapidly.

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CARDIOVASCULAR SYPHILIS

(a) **General.**—Cardiovascular syphilis in a medical clinic,²⁸ syphilitic aortitis,^{18 22 34 36} its pathology,²⁴ and the natural history of syphilitic heart disease^{29 30} have all been studied. Although the incidence of early syphilis in Morocco is seven times greater than in France, cardiovascular syphilis is comparatively much rarer.⁴ In an evaluation of 5,055 autopsies in South Carolina evidence of syphilitic involvement was found in 11.3 per cent. and rheumatic involvement in only 1.6 per cent. Cardiovascular syphilis was commoner in Negroes than in whites.²⁹ Of 43,429 persons examined in a community-wide survey in 1946, 739 had cardiovascular abnormalities, including 82 with cardiovascular syphilis. Nearly one-sixth of those thought to have syphilis had died within 3½ years.⁷

Of 141 cases of uncomplicated syphilitic aortitis, 15 per cent. developed aortic insufficiency after an average of 3½ years.³⁰ The natural history of aortic insufficiency, based on a study of 1,020 patients, has also been considered.³⁵

The stethogram has been used in combination with the electrocardiogram in the investigation of 161 patients.¹³ The stethogram proved of value in recording the aortic systolic murmur and the accentuated aortic second sound of cardiovascular syphilis. Phonocardiographic observations have also been made on the Austin Flint murmur.⁸ From a consideration of Foster's rule and *post-mortem* material it was thought hazardous to predict, either from the transmission of the murmur of aortic regurgitation or from the occurrence of the Flint murmur, which cusp is incompetent.²³ The ballistocardiogram has been used in aortic syphilis³¹: in aortic insufficiency there are usually large complexes with short I waves and deep K waves.

Thrombosis at the aortic bifurcation has been recorded in 35 cases, only one of which had syphilitic aortitis.² Myocardial infarction due to high grade stenosis of the coronary orifices²⁵ and descending myocarditis⁵ have also been reported.

A case of aortic aneurysm which ruptured into the pulmonary artery, on which a diagnosis was made before death,²⁶ has been reported. The literature has been reviewed and eighteen cases of aneurysm of the innominate artery, for which syphilis is invariably responsible, have been recorded,¹⁹ as have cases of syphilitic aneurysm of the subclavian⁹ and popliteal³² arteries.

(b) **Treatment.**—The penicillin treatment of cardiovascular syphilis has been considered by a number of authors.^{3 6 11 12 16} No progression of syphilitic heart disease was noted in 43 patients with simple aortitis treated with penicillin,¹⁴ but the results of 178 cases with complicated aortitis were less satisfactory.¹⁵ From a

statistical viewpoint there were too many difficulties in evaluating properly the penicillin treatment of cardiovascular syphilis from an examination of past records.¹⁰ Penicillin treatment has been given on an ambulatory basis and this procedure was considered safe provided that an examination of the cerebrospinal fluid was first made.¹² It has been considered desirable by some that patients with co-existent neurosyphilis should be treated as in-patients owing to possible dangers from Herxheimer reactions.¹¹

Alleviation of angina has been noted following the penicillin treatment of cardiovascular syphilis, although the addition of bismuth and mercury to the penicillin course is sometimes advised.²⁷ Penta erythritol tetranitrate was used in the treatment of angina but was found of little value.²³

The future treatment for the complications of syphilitic aortitis may well prove to be surgical, and striking progress is currently being made. The older surgical treatment of aneurysm by means of polythene wrapping, described as of value in twelve cases,²¹ is being replaced by excision of the sac. A brilliant surgical achievement has recently been described¹ whereby eight cases were so treated. One patient died and in one the complete operation was not possible, but the remainder were well. A syphilitic aneurysm of the third part of the subclavian artery was removed successfully,¹⁷ but after the removal of an aneurysm of the innominate artery the patient died.²⁰

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NEUROSYPHILIS

(a) **General.**—Lumbar puncture of 1,000 adequately treated syphilitics showed an abnormal spinal fluid in 177 cases.²⁶ About 5 per cent. of abnormalities were noted in 12,057 spinal fluids from cases of early syphilis.⁴ The prognostic importance of spinal fluid examinations after the follow-up of 428 syphilitics for 3–37 years in latency has also been reported.³⁸

That Negroes are more susceptible to syphilitic mental disease has been affirmed,²⁹ and the mental deterioration in G.P.I. has been considered in detail.²³ Electroencephalograms have been studied in various forms of neurosyphilis,¹ but the E.E.G. changes could not be correlated with the cerebrospinal fluid findings. Variations in the E.E.G. in an individual case have been noted.⁴⁷ Syphilis in mental deficiency has also been discussed. Only 2.4 per cent. of 1,331 mental defectives were believed to have been infected.²⁵ The Argyll-Robertson pupil has been considered in detail.^{3 7 19} Some signs of reversibility were claimed in three cases given sodium iodide, magnesium thiosulphate, thiamine, and a local anaesthetic intramuscularly.⁴⁰

The comparative rarity, tabes dorsalis in an African Negro, has been recorded,²¹ and 201 cases have been reported amongst Moslems in North Africa in whom it is also comparatively rare.³⁰ The theory of circulatory disturbance in tabes dorsalis has been advanced,⁴³ and the surgical aspects of the condition have been discussed,²⁴ as has the management of “cord bladder” by the operation of transurethral resection of the vesical neck.¹⁶ A further fatal case of masked perforation of a gastric ulcer in a tabetic has been reported.¹³ The occurrence of Charcot’s joints in diabetes mellitus, of

which about 25 cases have been reported in the literature, has also been considered.⁶ Of 6,442 persons legally declared blind in Ohio, syphilis was responsible in 507 cases, 67.7 per cent. of these being due to optic atrophy.¹⁷

Cases of gumma of the brain with hypothalamic symptoms,⁴⁴ of isolated softening of the dentate nucleus,⁵ of syphilitic internuclear palsy,⁴¹ of Parkinsonism apparently due to congenital syphilis,³⁶ of syphilitic disease involving the optic chiasma,⁵⁵ and of progressive bulbar palsy due to syphilis¹¹ have all been recorded. Syphilitic poliomyelitis has been considered⁴⁹ and the effect of electric convulsion therapy on treponemal antibodies in neurosyphilis has been studied.³³

(b) **Treatment.**—The results of the treatment of neurosyphilis with penicillin alone continue to be excellent.³⁷ On an experience of 102 patients with asymptomatic neurosyphilis it was recommended that 10 mega units should be given over 10 days.¹⁵ Observations on 69 paretic patients indicated that relapse or progression seldom occurred after 2 years following effective treatment, and that no more clinical improvement might be expected after the spinal fluid had become negative.¹² The cerebrospinal fluid levels of penicillin in sixteen cases of paresis treated with penicillin have been recorded.⁴⁸ Neurological and mental changes, believed to be due to the Herxheimer reaction, have been reported even after several injections of penicillin have been given.³⁴

The adherents of fever therapy have diminished considerably in number, although on a limited series of 52 patients with paresis it was considered that penicillin combined with malaria was the best treatment.⁹ A case of leucopenia occurring during fever therapy has been reported.²⁷ Chloramphenicol in daily doses of 1.5 to 2 g.—to a total 32 to 62 g.—was given with promising results in eleven cases,³² and to eight other cases also.⁴²

A case of tabetic crises treated with cortisone with apparently beneficial results has been recorded,⁵⁴ and there was some diminution of the frequency and severity of the lightning pains of five tabetics given adrenal cortical hormones.³⁵ Cortisone was also used in two patients with gastric crises, but the results could not be evaluated.³⁵ Mesantoin, in doses of 0.25 g. daily, proved successful in controlling convulsive seizures in neurosyphilis.⁵⁶

Penicillin alone was used in fifteen patients with optic atrophy, and 23 others were treated with penicillin plus malaria.²² There was a tendency for the condition to progress if the pre-treatment vision was worse than 6/20, but it was considered that malaria did not add enough to penicillin to justify its routine use in early syphilitic optic atrophy. On the other hand, in a study of 23 cases,⁸ combined fever was considered justifiable in some cases. In Japan injections of anterior pituitary hormone were made into the carotid artery in nine cases of optic atrophy, with some improvement in four; ² and ten other cases have been treated with placental extract.¹⁴

(c) **Cerebrospinal Fluid.**—It has been shown that lumbar puncture headache apparently does not depend on the actual withdrawal of cerebrospinal fluid.⁴⁶

The lipolytic activity of cerebrospinal fluid,¹⁸ and the behaviour of anti-treponemal and anti-lipoidal antibodies,³¹ have been considered. Positive agglutination reactions using spirochaetes from rabbits' testes have been obtained in Wassermann-positive spinal fluids.^{45 50}

The phase-contrast microscope has been used in the examination of cerebrospinal fluid cells.^{51 52} A total of 5,539 spinal fluids have been subjected to a battery of syphilitic tests; ³⁹ the V.D.R.L. test showed the best correlation with the cell count and protein estimation. The V.D.R.L. flocculation test was shown to be superior to the Kolmer complement-fixation test, particularly because of ease of performance.¹⁰ The use of the Meinicke reaction on contaminated fluids has been considered,⁵³ as have false positive serum tests for syphilis on the cerebrospinal fluid.²⁰ That the protein content may be elevated in diabetics when neurological complications are present has also been indicated.²⁸

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CONGENITAL SYPHILIS

(a) **Prenatal Syphilis.**—The causes of foetal and neonatal death, including congenital syphilis, have been discussed,¹ as has syphilis in pregnancy.^{13 37 48 51} In 1,002 syphilitic pregnant women treated between 1948 and 1950, the incidence of abortions, miscarriages, stillbirths, and neonatal deaths closely paralleled that in non-syphilitic women.⁵⁷ The use of penicillin in the prevention of congenital syphilis has been considered by a number of authors.^{2 5 6 47 65}

The decline in infantile mortality due to syphilis has been noted all over the world, and has been recorded, in particular, for Baltimore.³⁸ In Italy the total foetal loss due to syphilis has been reduced from 24 to 35 to 10 to 12 per cent., and the incidence of congenital syphilis from 56 to 1 to 2 per cent.⁵ On the other hand, reports have suggested that the incidence may be rising in

Germany.³³ In South Africa the status of 55 of 170 infants born to syphilitic mothers has been reviewed, the outcome of 53 being considered to be satisfactory.⁴³

In the majority of American states there are laws requiring serum tests for syphilis in pregnant women. A check on 16,017 pregnancies in North Carolina, however, indicated that only 54 per cent. had received such tests.⁶⁶ Other difficulties in the eradication of congenital syphilis have been discussed.⁶⁷

(b) **Early Congenital Syphilis.**—Infantile congenital syphilis has been considered in Singapore,⁵⁰ Germany,²⁵ and Italy.¹⁸ The social importance of congenital syphilis has been reviewed,²⁴ and some general observations concerning syphilis in children have been made.⁶⁴ Third-generation syphilis has been considered,^{8 45 68} and further instances of congenital syphilis in only one of twins have been reported.^{28 49} Other observations made include anaemia in congenital syphilis,³⁴ hepatic changes,¹⁷ infantile cataract,²¹ and platyspondylia in twins with congenital syphilis.⁵⁵

The epiphyseal growth in congenital syphilis has been considered;⁵⁶ skeletal changes were observed in eighty of 245 infants examined radiologically, of whom 238 were born to syphilitic mothers. Non-syphilitic changes consisting of transverse lines were observed in 74 cases and periosteal thickening in six.²³ In a consideration of 59 other cases,¹⁵ it was suggested that the typical changes in the skeleton in early congenital syphilis were due to growth disturbance, but that this did not apply in late congenital syphilis. Hutchinson's teeth have again been demonstrated radiologically before the eruption of the second dentition.⁶³ A positive meningeal reaction in a syphilitic infant has been recorded,²⁹ as has a fatal case of cerebral haemorrhage in a congenital syphilitic treated with penicillin.⁵³

The diagnosis of congenital syphilis has been discussed.^{35 46} Observations have been made indicating that in early congenital syphilis the Wassermann complement-fixation test becomes positive before the Kahn reaction.^{36 52} While differences in fractions of reagin have been considered responsible for this by some,⁵² others have postulated that it depends not on differences in the reagin but on the amount of it.³⁶

The treatment of congenital syphilis has been considered^{3 12} and one author has advanced the unorthodox view that all children born to syphilitic mothers should be treated even if sero-negative and healthy.¹⁶

(c) **Late Congenital Syphilis.**—Various aspects of late congenital syphilis have been discussed: teeth,^{7 26} nasal stigmata,⁹ and aural manifestations.^{10 27} Paroxysmal haemoglobinuria has also been considered;⁶¹ two types have been described: one with a positive serum test for syphilis and a positive Donath-Landsteiner reaction but with no cold agglutinins, and another in which these findings are reversed. A case of congenital tabes has also been described.⁴⁵ Five cases of acquired syphilis occurring in congenital syphilitics have been recorded.²²

Heredo-ocular syphilis has been considered.⁴⁴ Of blindness due to syphilis in Ohio, interstitial keratitis was responsible for 10.4 per cent.,²⁰ a follow-up for

an average of 8 years was obtained on 128 cases of interstitial keratitis; visual acuity was excellent in 30.6 per cent., good in 37.9 per cent., fair in 22.6 per cent., and poor in 5.6 per cent. In 2.4 per cent. only finger counting was possible, and 0.8 per cent. were blind.³⁹ Other ocular manifestations described include choroidoretinitis,³⁰ perforation of the macula,^{31 32} saucer-shaped brown atrophy of the lens,¹⁹ deep corneal inflammation,⁶² and the rare condition of Cogan's syndrome, or non-syphilitic interstitial keratitis with bilateral deafness, in this case associated with periarteritis nodosa.⁴²

The use of cortisone in syphilitic eye disease has been considered,⁴ and its use in interstitial keratitis has been reported by several authors.^{11 14 54 58 59 60} One report¹⁴ refers to eighteen cases successfully treated with cortisone drops or ointment. The use of penicillin, penicillin plus fever, and penicillin and fever plus cortisone have also been contrasted.⁴¹ The schedule employing cortisone gave the best results. A case of interstitial keratitis has been reported in which retinal phlebitis and choroiditis developed after several relapses.⁴⁰

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DIAGNOSTIC TESTS IN SYPHILIS

Agglutination and Immobilization Tests.—Advances in the diagnostic field occasioned by the treponemal immobilization test have led to new trials of agglutination tests for syphilis. X-ray irradiation has been used to inhibit antibody formation in rabbits infected with *T. pallidum*:^{1 19} treponemata from irradiated rabbits do not undergo spontaneous agglutination.

Such treponemata from irradiated rabbits have been used in an agglutination test on 122 T.P.I.-tested sera with remarkable agreement.¹ The agglutination test, moreover, was technically easier to perform than the T.P.I. test. Another agglutination test, using fresh ox serum which causes disappearance of spirochaetes and agglutination of sensitized sheep's cells, has been devised.¹⁶ Spirochaetal agglutination has also been considered by a number of authors.^{31 34 35}

In four papers, the originator of the T.P.I. test has reviewed his work in experimental syphilis since 1947.^{20 21 22 23} It was found that by mixing tissue-free suspensions of treponemata with syphilitic serum, exposing the mixture to heparinized whole blood, and incubating, the spirochaetes disappeared from the mixture, and that this did not happen when non-syphilitic serum was used. Preliminary studies have indicated that a specific antibody, separate from Wassermann reagin, is essential for this "disappearance phenomenon". Whether it can be used as a diagnostic test for syphilis has yet to be decided.

The use of the T.P.I. test is now being reported from many parts of the world: America,^{3 18 19 38} France,^{5 7 11 33 36 37} Denmark,^{26 30} and Canada.¹⁷ It has been found of particular value in the U.S. Navy in persons found to have a positive serum test for syphilis without other signs.²⁴ In one series of 783 T.P.I. tests, the reaction was positive in all of 37 patients with early latent syphilis and in 204 of 213 patients with late latent syphilis.¹⁸

The T.P.I. test has been used as a yardstick to assess the efficiency of standard serum tests, such as the Kahn verification test,⁸ and it will detect syphilis in all stages except early primary. It is highly specific except in yaws^{2 19} and the other treponematoses.²

Modified techniques for obtaining treponemata for inoculation have been described,⁶ and sensitivity has been increased by modifications in the treponemal concentration²⁸ and by the addition of sodium glycollate.^{25 27} Serum enriched media have also been used.³² The use of standard positive rabbit sera in liquid or dehydrated form for inter-laboratory control has been suggested.⁹ It has been demonstrated that rabbit syphilomata can be stored in the deep freeze and used after up to 12 weeks.⁴

The immobilizing antibody is avirulent¹² and animals other than rabbits have been shown to acquire it.¹³ It differs from the Donath-Lansteiner haemolysin¹⁰ and is removed by saturation with heat-killed spirochaetes.²⁹ Studies on the T.P.I. test in rabbits have been made after treatment with bismuth¹⁴ and penicillin.¹⁵

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Identification of the Treponeme.—The staining of *T. pallidum* with crystal violet and basic fuchsin dyes has been considered,¹⁰ and fountain-pen ink has been used.⁶ Unstained smears have been examined by dark-field illumination.^{3 4} By this means spheroid

bodies containing comma-like structures, comma-like bodies, and cysts containing numerous dense granules—believed to be stages in the life cycle of *T. pallidum*—have been observed.⁸ The phase-contrast¹² and electron microscopes^{1 2} have also been used. Under the latter many species of spirochaete were found to have one or more fibrils wound spirally round the body from one end to the other, sometimes outside and sometimes inside the cell membrane.²

A comparative study of treponemata found in the human genitalia, including *T. pallidum*, *T. microdentium*, and *T. macrodentium*, has been made.⁵ The metabolism of spirochaetes has been considered⁷ as have their nutritional requirements.¹¹ The breaking up of *T. pallidum* by ultrasonic vibrations has been investigated.¹³

Attempts at culturing the filtrates of the Nichols and Kazan strains of *T. pallidum*, and of *B. anserina*, failed to reveal any filterable forms,⁸ and attempts to cultivate the Nichols strain on embryonated hens' eggs have proved unsuccessful.⁹

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False Positive Reactions.—The incidence of false positive serum tests for syphilis has been reduced since the introduction of cardiolipin antigens. During a 15-year period using lipoidal antigens one laboratory had 0.47 per cent. false positive or doubtful results, whereas in 4 years with cardiolipin antigens their incidence was reduced to 0.16 per cent.¹⁴ The concept of the universal reaction, in which all sera are considered to contain some reagin, which spills over the diagnostic threshold in syphilis, and occasionally also in other diseases, has been reiterated,¹⁵ and some zone patterns have been studied.¹

Now that the T.P.I. test is available to show with certainty which are false positive results, research into the matter of false-positive reactors has gained fresh impetus. In a series of 300 persons giving only positive

serum tests for syphilis, reassessed in the light of the T.P.I. test findings, about 15 per cent. of the cases previously classified as having late latent syphilis proved to be false positive reactors, and 16 per cent. of those previously thought to be non-syphilitic were found to have syphilis.¹⁹ Apart from technical false positives, and so-called "acute false positives" of a temporary nature encountered in a number of conditions, it is considered that chronic false positive reactors often have serious underlying disease—in particular one of the collagen diseases. Of 51 such patients subjected to an intensive clinical and laboratory examination, it was shown that five had proved collagen disease; one each had sarcoid, Hodgkin's disease, and Gaucher's disease, and there was suspicious evidence of collagen disease in 21 others, and of sarcoid in two.²⁰ The collagen disease most likely to produce false positive results is disseminated lupus erythematosus, in which false positive serum tests for syphilis have been reported in 19 to 24 per cent. of cases.^{10 27} False positive serum tests may be noted years before the signs of lupus erythematosus appear.¹⁰

False positive reactions have been considered in general,⁸ and their high incidence in tropical climates noted.^{18 24 29} The incidence of false positive reactions has been discussed in leprosy,^{6 9 15 16 22 25} in virus pneumonia,¹² in brain diseases,³ after the intake of alcohol,⁵ and in Q-fever—in which 32 positives were noted in 427 persons tested.¹⁷ Positive serum tests were also reported in 183 of 1,226 sufferers from pulmonary tuberculosis.² A battery of serum tests for syphilis was performed on 130 volunteers inoculated with *P. vivax* malaria. The T.P.I. test showed no trend towards positivity and fewer positive results were noted when cardiolipin antigens were used instead of lipoidal antigens.²¹ A series of 104 patients has been studied after ether anaesthesia, but it was concluded that such anaesthesia was not a cause of false positive reactions³⁰ although it might bring about a reversal from negative to positive in a treated syphilitic. Likewise small-pox vaccination was not found to be a common cause of false positive reactions in infants.²⁶

No correlation between the results of liver function tests and false positive results has been noted,²⁸ but vitamin B given to patients or added to the sera *in vitro* may inhibit the Wassermann and Kahn reactions.⁷

After removal of alcohol-soluble lipoids, antigens can be prepared which do not react with syphilitic antibodies but do so with non-syphilitic ones.¹¹ Thus a verification test is theoretically possible.

The Neurath inhibition test has also been studied. This is based on the effect of a heat-soluble "inhibitor" fraction of serum on flocculation tests. Theoretically, false positive serum tests should be inhibited and true positives should be unaltered. It is concluded, as a result of studies in Guatemala, that the Neurath test added no significant information to that obtained by standard tests.⁴ In a comparison between the Neurath test and T.P.I. test with clinical diagnoses, much closer correlation was noted with the T.P.I. test than with the Neurath test.²³

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Standard Serum Tests.—The antibodies to syphilis have been discussed and three complement-fixing antibodies described.⁵⁶ A comprehensive review has been made of the properties of complement,²⁶ and the use of preserved complement has been reported.¹¹ Technical problems of complement-fixation have been considered.^{50 51}

An accurate technique for the preparation of a uniform sheep's cell suspension has been described,¹² and experiments with stored sheep's erythrocytes have been made.^{65 72} A comparison has been made of five methods of amboceptor production,⁴⁷ and the rapid inactivation

of sera has been considered.⁶ Although concentration of sera by evaporation did not increase sensitivity, dialysis through a semi-permeable membrane did so.⁵

Experiences with cardiolipin antigen,^{1 71} its use in quantitative techniques,⁷ and studies of its specificity⁷⁰ have been discussed, and tests with cardiolipin antigen have been compared with those with Mørch's antigen.⁶⁸ Zone phenomena with cardiolipin antigen have been studied.⁶² The standardized phosphatidic antigens in general have been discussed,⁷⁴ and Sitolipin, a phosphatidic acid obtained from wheat embryo, has been used as a syphilitic antigen.^{77 79 80} The use of egg-yolk lecithins has also been described.¹⁸ A protein antigen prepared from the Reiter treponeme, which is different from the polysaccharide and lipid antigens found in the body of the treponeme, has been tried.¹⁵ A new nitrogen-containing antigen obtained from beef-heart has also been used.⁷⁸

In some countries, e.g., Germany, the precise serum test for syphilis is prescribed by law.⁷⁵ It is now queried whether, in the light of new developments with cardiolipin, the law should be changed.

A very detailed consideration has been made of the Wassermann test,³¹ and with cardiolipin.^{3 40 41 42 53 54 69} Anticomplementary reactions have also been discussed.^{39 55} A Wassermann screening test with standardized reagents but with only one tube has been described,¹⁰ as has a modification with dilute antigen for detecting false positive results.⁶⁰

The V.D.R.L. test has been considered by a number of writers,^{8 9 16 17} as have the effects of temperature on the test,^{8 22} and a capillary tube technique for the collection of specimens.²⁰ A study was made of 3,149 patients with negative Kahn and positive V.D.R.L. reactions: ⁴⁸ 1,746 of these patients required treatment, 11.4 per cent. having a positive cerebrospinal fluid and 14.7 per cent. some complication of syphilis.

The V.D.R.L. test has been shown to be less rapid in becoming positive in primary syphilis than the Mazzini flocculation test,¹⁴ although the V.D.R.L. and the Kolmer gave fewer false positive reactions than the Kahn and Mazzini.³⁸ A study has been made of the rate of reversal to sero-negativity of a number of tests after the treatment of early syphilis,¹³ and a number of serum tests have been described.⁴⁹ Quantitative serum tests,^{2 76} diagnostic problems when re-treatment is in doubt,⁵⁸ and the interpretation of serum tests have been discussed.³²

Much work has been directed to the evolution of simpler tests: Behring,⁸¹ von Boros,^{52 82} Bram's fresh blood test,²¹ Chediak,^{28 63 66} Citrochol,⁶¹ F.P.M.,²⁷ Howard,³⁰ Kahn with cardiolipin,⁸³ Kline,⁶⁷ Ko Da Gou,⁴⁶ Kolmer with improved cardiolipin,^{25 35} Laughlen,⁵⁷ Mazzini cardiolipin flocculation,⁴ Meinicke,^{23 36 67} modified Meinicke with dried blood,^{19 64} Meinicke II with cardiolipin,⁴⁵ Price precipitation test,⁴³ Rein-Bossak,^{29 44} Suchet,³⁷ and a Russian slide test using "universal" antigen.⁵⁹

The use of dropping pipettes for the Kahn test³³ and three different mechanical rotators for the Kline test³⁴ have been described.

Skin Tests.—An intradermal reaction employing cryolysate of Reiter spirochaete has been considered,²⁴ and a formolized suspension has been used⁷³ which gave no positives in 74 controls or in seven patients with primary syphilis, but predominantly positive results in the later stages of the disease. No correlation was noted between the results of the skin test, serum tests, and T.P.I. test.⁷³

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THE TREPONEMATOSES

The whole question of the treponematoses has been considered⁶⁷ as has the possibility of four treponemata from a single source.³⁰ The radesyge of Norway in 1710–1850 has also received attention.⁶

Endemic Syphilis.—Bantu syphilis in South Africa has been described⁵⁵ and the bone lesions of endemic syphilis of Bechuanaland illustrated.⁴⁴ Syphilis in the Niger Province of French West Africa has been stated to be largely extra-venereal.⁴³

The clinical aspects of bejel in Iraq have been discussed⁴ and a case of severely mutilating bejel has been reported.³¹ The disease also exists in adjacent Saudi Arabia under the name "balash".²

The endemic syphilis of Bosnia has been comprehensively reviewed.¹⁴ It was noted that in villages where there were numerous fresh cases there were often numerous gummata also, and it has been postulated that the latter may have arisen from superinfection of latent cases, the lesions being related to the time interval since the first infection. The behaviour of treponemes from Bosnian syphilis in rabbits^{60 61} was found to resemble that of venereal syphilis rather than that of yaws. The incidence of neurological involvement in endemic syphilis in Anatolia has also been studied.⁴¹

Acquired syphilis in children in India has been reviewed,⁶⁶ and endemic syphilis similar to bejel and the njovera of Southern Rhodesia has been reported in Madras.⁴⁷ The mass treatment of syphilis in an Indian Province has been considered.⁵

Pinta.—A study of pinta has been made in the Tepalcatepec basin of Michoacan, Mexico.^{9 10 11 12} Further epidemiological data on Mexican pinta have been presented⁶³ and 460 cases described.⁶² The pattern of Kahn's universal reaction in Mexican pinta was identical with that of syphilis and similar to but not identical with that of yaws.³³ The satisfactory effects of penicillin in pinta have been noted.⁵¹

Yaws.—The nomenclature of yaws has been considered.⁸⁴ The First International Yaws Symposium held at Bangkok in 1952 under W.H.O. auspices has been reviewed¹⁹ as has the progress of W.H.O.-assisted anti-yaws campaigns.^{53 68} In these it has been found important to examine as near to 100 per cent. of the population as possible and to treat all contacts even if apparently uninfected. Re-surveys of the entire population at intervals of approximately 6 months to a year are also necessary. The numbers involved in the six major W.H.O.-assisted campaigns against the treponematoses now total 9,454,925 examined and 3,163,353 treated.

The extent of the yaws problem in Africa²⁰ and in French Africa⁶⁴ has been reviewed in detail, as has yaws in Brazil,^{15 16} and in Guam,⁵⁴ and the W.H.O. campaigns in Haiti,⁴⁵ Indonesia,^{25 57} Thailand, and the Philippines. In the latter three countries prevalence rates of 15.3, 5.8, and 13.0 per cent. respectively were encountered.²⁵ The planning of yaws control in S.E. Asia has also been considered.³² One hundred cases of yaws in the State of Hyderabad have been described,⁴⁸ and observations have been made on yaws in Portuguese territories overseas,⁸ and in Western Samoa.⁴² Ancient bones discovered in the Marianas indicate that yaws existed there before the introduction of syphilis.⁵⁸

Climatic and geographical factors in the aetiology of yaws have been considered.²⁶ That a minimal humidity is needed is indicated from observations in French Equatorial Africa.³⁶ The possibility of the transmission of yaws by wound-feeding diptera has been reinforced by further experiments.⁵⁶ The natural history of the disease has been described.²¹ Secondary cases can apparently occur after some years of latency. A case of polydactylitis and periostitis of the forearm bones has been recorded.⁶⁵ The concentration of total non-protein nitrogen and total free amino-acid nitrogen has been found to be low in yaws.¹³ The first case of juxta-articular nodes in China has been reported.³⁹

Diagnostic aids in the mass treatment of yaws have been considered,^{49 50} and the use of quantitative serum tests recommended.⁷ Penicillin-sensitivity tests of yaws treponemata and cross-immunity experiments with the Nichols strain of *T. pallidum* have been described,⁶¹ and the time-dose relationship of penicillin therapy has been discussed.^{35 52} It is calculated that a detectable blood level of penicillin should be maintained for a minimum of 96 hrs, and that this can easily be achieved by a single injection of a repository penicillin. In rabbits the 50 per cent. curative dose is estimated at 16,000 units/kg.⁴⁹

The principles of yaws control have been discussed²² as well as the mass treatment of treponemal diseases in general.¹⁷ The results of treating 636 cases of yaws on an experimental schedule of only 600,000 units of P.A.M. have been presented.^{37 38} Although this dose was said to be sufficient, it represents but a fraction of the dosage of penicillin usually given in the W.H.O.-assisted programmes.⁶⁹ The use of aureomycin,^{27 28 29} chloramphenicol,^{15 18 27 28} and terramycin^{27 28 29} in yaws has been described. Although the results were good, treatment by injection was preferred. Stovarsol was given orally in New Guinea.⁴⁶

The success or otherwise of the mass treatment schemes depends on their ultimate integration with the existing health structure. This so-called "consolidation phase" has been considered in Africa,²³ and in the Philippines.³ The opportunity of yaws control to act as a spearhead to promote rural health services has been discussed,⁵⁹ as has the role in yaws control of W.H.O.¹ and U.N.I.C.E.F.³⁴

The new benzathine penicillins have considerable application to mass treatment programmes. It is obviously impracticable literally to treat a given area "simultaneously", as the process must take some time during which there is always the danger that treated cases may be re-infected from untreated cases. With the very prolonged penicillin serum levels now possible, a much greater number of persons can have penicillin circulating in the blood stream at any one time.

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VENEREAL DISEASE CONTROL

(a) **General.**—The origin and antiquity of syphilis²², its treatment through the ages,⁸ the medical history of the four voyages of Columbus,¹² venereal diseases in the Bible,³⁵ and in the writings of Shakespeare,²⁵ ³³ early contraceptive sheaths,¹⁵ and the itinerant women venereologists of Germany during the 15th to 19th centuries,⁴⁵ have all been considered. Half a century of international venereal diseases has been reviewed,⁵ and an obituary notice of Bernard Dattner who died in 1952 of cerebral tumour has been published.⁵⁰

Venereal disease control in the U.S.A. has been discussed.³ ⁶ ¹⁴ ⁵¹ The number of cases of early syphilis has declined from about 200,000 in 1947 to approximately 50,000 cases annually, although it is estimated that about two million persons suffer from late or latent syphilis, of whom approximately 250,000 will, if untreated, develop late manifestations.⁶ It has been stipulated that this decline has caused undue optimism in some quarters and undue scepticism in others, and that the truth lies somewhere between the two extremes.⁴⁹ Adjustment to the antibiotic era of venereal disease control¹⁰ ¹¹ ⁴⁷ and likewise of therapy⁵² has been considered, but there is no foreseeable termination to venereal disease control measures short of the extinction of the causative organisms at home and abroad.⁴

Much venereal disease in the U.S.A. is treated by private physicians. As a result of a questionnaire sent to 4,236 physicians in Philadelphia, it was calculated that, had all cases been notified to the Health Department, the reported incidence of syphilis would have increased by 59.9 per cent. and that of gonorrhoea by 70.1 per cent.²⁸

With the decline in the incidence of syphilis, mass serum testing is proving an expensive method of case-finding and concentration on special population groups has been recommended.³⁶ The cost per case discovered by pre-marital testing in California has been estimated at 1,298 dollars,⁹ although statisticians calculated that even at this high figure money was still being saved for the State. The local organization of testing stations in an urban area has also been considered.³² ⁴⁸

(b) **Social Aspects.**—Venereal disease control has been considered in Canada,⁷ ³⁹ amongst North American Indians,¹³ amongst U.S. forces in the Far East,²¹ and in Mexico.¹⁸ The social pathology of

syphilis in the Bantu has been studied.⁴⁴ Syphilis results from promiscuity, and the latter arises directly from unsatisfactory living conditions. Social and medical data on syphilis in and around Utrecht in World War II⁵⁴ and the V.D. education of the U.S. Navy¹ have been reported.

The declining incidence of double infections of gonorrhoea and syphilis in Copenhagen has been noted.²⁴ An investigation into the contacts of syphilis has been made.³¹ Such contacts, even if non-infected are susceptible to venereal diseases.⁴⁶ The sources of venereal infections in Finland have been discussed.³⁸ The worthwhile results obtained by pursuing contacts of military cases have been emphasized¹⁶ ³⁴ and trained nurses have been found more successful in obtaining information than relatively untrained military personnel.¹⁷ Further observations have been made on defaulters.²³

Prostitution in the U.S.A. over four decades²⁶ and the rehabilitation of prostitutes⁴¹ have been discussed. In Japan prostitutes have formed themselves into a trade union to prevent exploitation by the brothel owners.²¹

(c) **World Activities.**—Syphilis has been studied in Brazil,²⁰ amongst school children in Guatemala,¹⁹ in Western Germany and Western Berlin,⁴² in Porto Rico,⁴⁰ in Somaliland,²⁹ and in Tahiti.³⁰ A venereal disease survey has been carried out at Sokoto, N. Nigeria,⁴³ and a combined health education and venereal disease project has been conducted at Edfa in Upper Egypt.⁵³ A 60-day programme was instituted in the U.S. Virgin Islands, in which 12,750 residents were serum-tested, and all persons tested, regardless of evidence of infection, were given an injection of repository penicillin.³⁷

(d) **Prophylaxis.**—Cultivated treponemata have been shown to be highly susceptible to soap, but susceptibility was not increased by adding 2 per cent. hexachlorophene.²⁵ In an experiment of oral chemoprophylaxis (abortive treatment) involving 12,000 U.S. servicemen, there was a 58 per cent. reduction in the incidence of gonorrhoea when 200,000 units of penicillin was given 14 hrs after exposure to risk of infection, but a 75 to 100 per cent. reduction could be obtained if penicillin was given immediately after the risk. Masked syphilis did not appear to be a problem.² Nine cases of allergic dermatitis due to the prophylactic kit for local use have been reported.²⁷

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NOTE

For the past seven years the author has contributed an annual review of the literature to the *Bulletin of Hygiene* under the title "Perspectives in Venereology". The first five reviews and parts of the sixth were re-written and published in book form in 1953 under the title of "Progress in Venereology" (Heinemann, London; reviewed in the *British Journal of Venereal Diseases*, **29**, 242). The foregoing paper supplements the book. For the sake of brevity all names have been omitted from the text, and listed alphabetically at the end of each section.

For easier reference to the work of particular authors in various fields, a further complete alphabetical index is appended, showing the pages on which details of their publications appear.

The papers referred to have all been published or abstracted in the *American Journal of Syphilis*, *Gonorrhea*, and *Venereal Diseases*, *British Journal of Venereal Diseases*, *Bulletin of Hygiene*, *Abstracts of World Medicine*, or *Bulletin of the World Health Organization*. The author is indebted to the Venereal Diseases Division of the United States Public Health Service and to the World Health Organization for lists of references.

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