ABSTRACTS

This section of the JOURNAL is published in collaboration with the two abstracting Journals, ABSTRACTS OF WORLD MEDICINE and OPHTHALMIC LITERATURE, published by the British Medical Association. The abstracts are divided into the following sections: Syphilis (Clinical, Therapy, Serology, Pathology, Experimental), Gonorrhoea, Non-Gonococcal Urethritis and Allied Conditions, Chemotherapy, Public Health and Social Aspects, Miscellaneous. After each subsection of abstracts follows a list of articles that have been noted but not abstracted. All subsections will not necessarily be represented in each issue.

SYphilis (Clinical)


Of 550 patients with tertiary syphilis seen and treated within the Lille district in the years 1945 to 1960, 495 (90 per cent.) had neurosyphilis. Despite the general reduction in the incidence of primary and secondary syphilis there has been a relative increase in the incidence of tertiary syphilis and a marked preponderance of neurosyphilis, not entirely due to better diagnosis. It is contended that the increased frequency is in part due to inadequate therapy of early syphilis—largely owing to the use of too low a penicillin dosage without ancillary treatment with bismuth. Of the patients with neurosyphilis, 165 (32 per cent.) had tabes dorsalis, 176 (35 per cent.) general paralysis of the insane (G.P.I.), and 106 (21 per cent.) the meningo-vascular type. The male:female ratio was 2:1. Only 51 (12 per cent.) gave a history of primary or secondary lesions (but this figure is not dependable in view of the known difficulty of obtaining a history from the patient with G.P.I.). Of these, only in one-fifth did the tertiary disease develop within 10 years of the primary lesion and in 44 per cent. the interval was more than 20 years. It is important to note that 29 per cent. of these patients had received no treatment, while the rest had had very erratic penicillin or metallotherapy, quite inadequate for total resolution. This is in contrast to the findings in a group of patients in whom early syphilis had been adequately treated and of whom none had developed tertiary syphilis after 15 years. In 75 per cent. of cases the patients in this group had been given over 20 mega units of penicillin, usually with concomitant bismuth therapy for 3 months. All had had the course repeated at least once in 3 years and usually until the serology had become normal.

The patients with tertiary syphilis were treated with penicillin in doses ranging from 10 to more than 100 mega units. Clinically, the effects of treatment once the third stage was established were rather disappointing. Of the patients with classical tabes, few showed any improvement in the objective signs such as areflexia, trophic changes, or hypertonia, but on the other hand lightening pains and visceral crises were often relieved. Among the paralytics only stabilization of the condition was achieved, although oculomotor abnormalities often cleared up, with the exception of the persistent Argyll Robertson pupil. In about 60 per cent. of cases the serology became normal, while in a further 30 per cent. it was improved. Here the good effect of penicillin on cytological response was noted. A similar pattern of response in other forms of tertiary syphilis was observed, notably a reduction in the incidence of severe aneurysms and interstitial keratitis.

A major problem presented was the frequency with which serologically negative tertiary syphilis was encountered with clinically obvious involvement. Here the treponemal immobilization (Nelson) test proved invaluable, but the fact is emphasized that inadequate therapy will very often improve the serology in the early stages, yet will not prevent the eventual evolution of the severe tertiary stage. Once this is established little can be done to resolve the damage.

Allene Scott


A survey of the incidence of syphilis amongst eye cases in two large cities in Ceylon was made and the results are compared. A brief review of the opthalmic aspects of syphilis is included.

L. Weerekoon


The author suggests that the illness produces a thickening of the perilamin membrane; a slight trauma will then be sufficient to break it and to give place to keratitis.

J. Sosa Cazes


In a case of hypertrophic neuritis with the Argyll Robertson sign, the authors stress the impairment of the ciliary nerves with a normal pellucidum cap; this observation favours the hypothesis of the peripheral origin of the Argyll Robertson sign.

Vallon

The ocular signs were dilatation and tortuosity of the retinal veins, perivascular haloes, and a haemorrhage on the temporal side. *J. Sosa Caéales*


**SYPHILIS (Therapy)**


Penicillin has proved so effective in the treatment of syphilis that experience with other antibiotics in this disease is very limited. Most published series have been very small so that evidence of the efficacy of these substances in treatment is scanty. The author of this paper, who works at the Skin Clinic of the Karl Marx University, Leipzig, reports his findings after treating twelve syphilitic patients with erythromycin. One patient had sero-negative primary syphilis, four sero-positive primary syphilis, two early secondary syphilis, and five advanced or relapsing secondary syphilis.

The dosage of erythromycin varied from 1·0 to 1·6 g. daily and this was continued for 15 to 20 days. *Treponema pallidum* disappeared from all primary lesions within 45 hours and was not detected again. The secondary lesions cleared up in a similar manner to that seen after the usual penicillin treatment. The effect of treatment on the serological tests was somewhat less impressive. The case of sero-negative primary syphilis became sero-positive one week after completing treatment, but returned to negative again within 4 weeks. The other cases of sero-positive primary syphilis all became sero-negative within 1 to 5 months after treatment. Of the five cases of secondary syphilis, only one became sero-negative during the follow-up period of 7 months. The author suggests that a longer period of administration of the drug may be required in such cases.

An interesting discrepancy between the concentration of erythromycin required to produce immobilization of *T. pallidum* in *vitro* and the serum levels required to produce clinical cure is pointed out. *In vitro* a concentration of 2,700 μg. per ml is required (compared with 0·01 μg. per ml with penicillin), whereas the serum levels obtained with the dosage used were of the order of 5 to 20 μg. per ml. The explanation is not apparent.

The indications for erythromycin in syphilis are discussed and the author concludes that it has a place in the treatment of those sensitive to penicillin. *R. D. Catterall*


It has been known since 1953 that erythromycin has treponemidal properties, but there have been few clinical studies of this antibiotic. Erythromycin is a satisfactory antisyphilitic agent in large doses and this article from Baylor University College of Medicine, Houston, Texas, records an attempt to find the minimum dosage required to yield a satisfactory cure rate. A total of 148 dark-field positive cases of syphilis were studied, erythromycin stearate and propionate being used in six schemes of dosage. The period of observation was too short for some of the higher dosage schedules to permit a definite conclusion to be reached, but very encouraging results were obtained with a dosage of 2 g. erythromycin stearate daily for 10 days, only 5 per cent. of patients requiring re-treatment within 6 months. 3-day (9-g.) and 5-day (10-g.) schedules were definitely inadequate; 1 g. erythromycin propionate given daily for 10 days gave better, but not very satisfactory, results.

[This drug may provide a useful method of treatment of early syphilis in patients who do not tolerate penicillin.]

Robert Lees

**Treatment of Neurosyphilis with Antibiotics.** (Tratamiento de la neurosifilis con antibióticos.) Orlande, R. (1960). *Pren. méd. argent.*, 47, 3182. 49 refs.


SYPHILIS (Serology)

In common with recent experience in many countries the number of cases of early syphilis seen at the University Dermatological Clinic, Munich, since 1958 has markedly increased. The author notes that from past experience it can be expected that the incidence of congenital syphilis will also increase in due course. It is therefore now particularly important to test pregnant women for the presence of latent syphilis. At the Munich Clinic, 11,153 sera of pregnant women were tested antenatally between 1951 and 1956 by the Meinicke reaction; if the result was positive a number of other standard serological tests, and in special cases the treponemal immobilization (T.P.I.) test, were also performed.

In all, 42 of the women (0.38 per cent. of the total tested), were found to be suffering from latent syphilis. In three mothers the standard reactions gave a negative result, but the children developed late congenital syphilis; on re-testing these mothers by the T.P.I. test the result was found to be positive. It is suggested that all women with previously treated syphilis should receive penicillin during each subsequent pregnancy, the only exception being patients in whom the response to the T.P.I. test has become negative.

G. W. Csonka


The Reiter protein complement-fixation (R.P.C.F.) test has been adopted by the Massachusetts Department of Public Health, Boston, as a screening procedure for patients in whom the Hinton test for syphilis has given a positive result. If the R.P.C.F. test also gives a positive reaction the diagnosis of syphilis is held to be confirmed; if negative, a treponemal immobilization (T.P.I.) test is advised. This report describes the results of tests on 703 patients (310 male and 393 female) with persistently positive results by the Hinton test but who presented no clinical, historical, or epidemiological evidence of syphilis. The series consisted of 548 clinic or hospital patients and 155 private patients, and 478 were white and 225 Negroes.

Patients were classified as syphilitic if either the T.P.I. or the R.P.C.F. test, or both, were positive, and as biological false positive (B.F.P.) reactors if both the treponemal tests gave a negative result. On this serological evidence 548 patients were judged to have syphilis and the other 155 were thought to be B.F.P. reactors. It was noted that syphilis was commoner in married or divorced patients of both sexes than in those who were single, in clinic (82.3 per cent.) than in private patients (63 per cent.), and in coloured (96.4 per cent.) than in white patients (69.2 per cent.). The infection rate was about the same in the two sexes in each race respectively. Analysis by age showed that in the white patients the incidence of syphilitic reactions increased in frequency from 20 to 24 up to about 45 years of age, after which it tended to level off, but this sharp decrease did not occur in the non-white patients. The greatest incidence of B.F.P. reactions was found in the 15 to 19 age group, in which 75 per cent. of the positive Hinton reactions were classed as non-specific; these were commoner in females.

It is noted that most of the Hinton test results thought to be non-specific were only positive at a low titre ("doubtful" or positive with undiluted serum), the highest titre observed being 1 in 16. It is stressed that reagin tests are still of value in the diagnosis of syphilis since in over 80 per cent. of the patients whose sera gave persistently positive results by the Hinton test the diagnosis was confirmed by the response to the more specific treponemal tests.

A. E. Wilkinson


It has previously been found that some rubber stoppers are responsible for test sera becoming toxic and so affecting the results of the treponemal immobilization (T.P.I.) test. In the present study, carried out at the University Skin Clinic, Jena, it was shown that not all rubber stoppers have this effect and that 100 per cent. immobilization of the treponemes occurred only in the presence of certain vulcanization accelerators used in the manufacture of some stoppers. Rubber stoppers not containing these accelerators could be used without ill effect on the sera used in the T.P.I. test.

Until rubber which does not contain these harmful chemicals is universally available it is considered advisable to use stoppers made of natural cork. G. W. Csonka


A new means of serological diagnosis of syphilis in the form of the immunofluorescent technique is described. In the direct method of Coons and others (J. Immunol., 1942, 45, 159) as applied to syphilis by Deacon and others (Proc. Soc. exp. Biol. (N.Y.), 1957, 96, 477; Abstr. Wild Med., 1958, 24, 26) treponemal antibody combines on a glass slide with a treponemal suspension. The resulting antigen-antibody complex is invisible, but can be revealed by treatment with antitoglobulin combined with fluorescein isothiocyanate. In the direct method the antibody in the serum is combined with fluorescein. This method, however, is less sensitive and requires the conjugation of each serum with the dye. The fluorescent treponemal antibody
test compares favourably with the V.D.R.L., Reiter protein complement fixation and treponemal immobilization tests, particularly in primary syphilis.

The preparation of the reagents for this test is described in adequate detail. The antigen is a treponeme of Nichols strain obtained from intratesticular culture in rabbits. Anti-human globulin is prepared by the immunization of goats or rabbits, the final concentration of antibody lying between 400 and 700 µg. N per ml. The proper conjugation of the Coombs reagent with fluorescent dye is highly critical and not all brands of fluorescein are suitable. It is carried out at 0°C. under magnetic stirring and 0-05 mg. of solid dye is added for each milligramme of protein in the solution and then stirred for 16 to 18 hours at 2 to 4°C. At the end of this period excess dye is removed by dialysis or other methods. A simple titration against a positive test serum is then carried out to determine the optimum dilution of the fluorescein-treated Coombs reagent.

The patients' serum for the test is inactivated and used in a 1:50 dilution in buffered saline. For the test itself two 0-01-ml amounts of treponemal suspension are applied to a slide and dried at 37°C. under constant agitation to ensure an even distribution of treponemata within previously marked circles. The treponemal film is fixed in acetone for 10 minutes and 0-03 ml of the 1:50 serum then applied at 37°C. for 30 minutes under constant agitation. This is followed by two rinses and then the application of the fluorescein-antiglobulin reagent in the same way as the serum was applied. The optical equipment for reading the test is briefly described. At first the presence of treponemata is confirmed under simple dark-ground illumination and then the reading proper is performed under ultraviolet light in duplicate on the two inocula on each slide, and graded from ++ + to —.

This paper is preceded by a companion paper by the same authors dealing with the fundamental aspects of the immunofluorescent technique. F. Hillman


Sera submitted for serological tests for syphilis (S.T.S.) were examined for evidence of Brucella infection at the University of California School of Medicine. Agglutination tests using Br. abortus suspensions prepared by the Bureau of Animal Industry of the U.S. Department of Agriculture were performed by the technique recommended by the Committee on Brucellosis of the National Research Council. All specimens were subjected to treponemal immobilization (T.P.I.) tests, V.D.R.L. slide tests, and Kolmer cardiolipin complement fixation tests. Brucella agglutinins ranging in titre from 1:20 to 1:5,120 were found in 21-1 per cent. of 464 sera which gave positive T.P.I. and S.T.S. results (syphilis group) and in 29 per cent. of 1,126 sera giving positive S.T.S. but negative T.P.I. reactions (biological false positive (B.F.P.) group), but in only 10-4 per cent. of 444 sera from patients classed as normal whose sera gave negative results with both the S.T.S. and T.P.I. test. [The patients appear to have been classified on purely serological grounds, and no indication is given of the distribution of the agglutinin titres found in the three groups.]

Intradermal tests using a commercial reagent ("brucellergen") were also performed on 278 patients; positive reactions were found in twelve out of 33 in the syphilitic group and 21 out of 45 in the B.F.P. group, but in only nineteen out of 200 “normal” patients tested.

The results are thought to show a significant relationship between past or present Brucella infection and the presence of reagin. Tests on sera from some B.F.P. reactors showed that reagin can be absorbed from serum by Br. abortus. It is suggested that reagin may be formed in response to Brucella and perhaps other infectious agents as well as to Treponema pallidum. Failure to obtain sero-reversal in patients who have been adequately treated for syphilis might be due to a concurrent Brucella infection. A. E. Wilkinson


In the syphils serological laboratory of the New York City Department of Health 100,000 samples of blood have been screened for antibody to cardiolipin antigen by both the V.D.R.L. slide technique and the unheated serum reagin (USR) slide test. The tests gave the same results with 98.2 per cent. of the sera. As the U.S.R. test is the simpler the authors recommend its use as a screening procedure in laboratories dealing with large numbers of sera.

All sera found to be positive were then tested by the Kolmer complement fixation test and over 1,000 samples were also titrated for complement fixation with Reiter protein antigen and with Treponema pallidum antigen (T.P.C.F. 50). The former test was similar in reactivity to the latter and is less expensive. Janice Taverne


A series of 54 patients (36 women and 18 men) attending or referred to the Whitechapel Clinic of the London Hospital were found to have persistent non-syphilitic reactions to the classic serological tests for syphilis. They had no past history or clinical evidence of syphilis, and the treponemal immobilization test gave negative results in all cases. These patients were observed for 1 to 5 years and were subjected repeatedly to haematological studies, estimation of the plasma total protein and albumin and globulin levels and of the serum cholesterol level, and investigation of their peripheral blood for the presence of L.E. cells.

During observations six of the women developed systemic lupus erythematosus with L.E. cells in the peripheral blood, one dying, while one of the men died of periarteritis nodosa. In addition nine women and five men developed discoid lupus erythematosus or other possible collagen diseases without L.E. cells and twelve women and four men had various haematological
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At the Institute of Venereology, Madras Medical College, the sensitivity and specificity of the Treponema pallidum agglutination (T.P.A.) test were compared with those of three standard tests in which lipoidal antigens are used—namely, the V.D.R.L. slide test, the Kahn test, and the Wassermann test. The T.P.A. test was carried out according to the technique of Hardy and Nell (J. exp. Med., 1955, 101, 367; Abstr. Wild Med., 1955, 18, 462) except that sera were not absorbed with lipoidal antigen before testing.

The sensitivity of the T.P.A. test was evaluated by examining specimens of serum from 216 cases of untreated syphilis in various stages. Positive reactions to the T.P.A. test were obtained in 97-7 per cent. of the cases, the figures for the other tests being V.D.R.L. 99-5 per cent., Kahn 98 per cent., and Wassermann 99 per cent. The sensitivity of the tests was much lower with sera from patients with treated syphilis, positive results to the T.P.A. test being obtained in 53-7 per cent. and with the V.D.R.L. in 78 per cent. This was probably due to the large number of patients (57) with treated early infections who were included in this group.

Specimens of serum were also tested from 176 healthy individuals and 539 patients with various conditions, including 42 with venereal diseases other than syphilis and 332 with leprosy. On the assumption that none of these patients had syphilis, the T.P.A. test was non-reactive in 96-8 per cent., the V.D.R.L. in 92-6 per cent., the Kahn in 92-3 per cent., and the Wassermann in 72-7 per cent. No definite diagnosis could be established in fifteen cases in which sera gave positive reactions to all four tests. No positive reactions to the T.P.A. test were obtained in the group of 176 healthy subjects.

The T.P.A. test was carried out before and after absorption of 247 sera with V.D.R.L. antigen to remove reagin antibody. This produced a reversal to negative of the T.P.A. response which had been positive with unabsorbed serum in eight out of 137 syphilitic sera, in seven out of 65 sera from cases of latent syphilis where the diagnosis was supported by other than serological evidence, and in two out of 33 in which the diagnosis of latent syphilis was serological only. Reversal also occurred in tests on ten out of twelve sera from patients in the non-syphilitic group. Although the absorption technique presumably reveals a specific antibody distinct from reagin, the authors do not consider that it is very practical for routine use.

Tests were repeated at intervals up to a year on five positive and five negative sera, the same treponeme suspension being used throughout. The results were reproducible and the antigen appeared to be stable over this period when stored at 5° C.

The authors conclude that the T.P.A. test in the form used in this investigation cannot be regarded as a substitute for the T. pallidum immobilization test, but that it merits further study directed towards the development of an antigen which is agglutinated only by the specific treponemal antibody and not by reagin. A. E. Wilkinson


The results of the treponemal immobilization (T.P.I.) test, performed at the Institut Alfred Fournier, Paris, on 2,339 samples of human serum, were compared with the results of complement fixation tests performed with cardiolipin and with antigens from Reiter's treponeme and from the Nichols strain of Treponema pallidum, both obtained by disruption with ultrasonic vibrations. In 41 per cent. of the cases the results of the four tests failed to agree; 856 were positive by the T.P.I. test, 727 with the Nichols antigen, 628 with the Reiter antigen, and 150 with the lipid antigen. Among 79 sera giving false positive results with lipid, 53 also did so with the Reiter antigen, but only 36 did so with the Nichols antigen. Thus it appeared that, next to the T.P.I. test, the complement fixation test with the ultrasonically disrupted Nichols strain was the most sensitive and most specific test.

The T.P.I. test and the complement fixation test with cardiolipin gave negative results with 24 sera from patients with primary syphilis; nine were positive with the Nichols antigen and all were positive with the Reiter antigen, indicating that this last test detected the presence of antibody at an earlier stage than the rest. When the four tests were performed on 345 samples of cerebrospinal fluid the T.P.I. reaction was found to be positive in cases of progressive syphilis of the central nervous system, but negative in stabilized or cured cases, for which tests performed with the ultrasonically prepared antigens were more sensitive.

Results obtained with sera from laboratory animals which had been inoculated with living or ultrasonically disrupted cultures of the Nichols strain or with disrupted cultures of Reiter's treponeme suggested that immobilizing antibodies differ from complement-fixing antibodies and that the antibodies reacting with ultrasonically prepared Reiter and Nichols antigens differed not only from those reacting with lipids, but also from each other.

Janice Taverne


Since 1952 many tests have been introduced in the
attempt to remedy the inadequacy of the routine serological tests for syphilis, which have a range of positivity of only between 30 and 68 per cent. The development of the V.D.R.L. and cardiolipin antigens has helped to raise the proportion of positive results above 70 per cent. and the treponemal immobilization (T.P.I.) test of Nelson may give up to 98 per cent. positive reactions in syphilis. However, even this last test gives poor results in osseous syphilis and in tabes. The luetin intradermal test was reported by Degos in 1944 to give 100 per cent. positive results in tertiary syphilis when Muller’s organic luetin was used in place of Noguchi’s culture product. The present authors have examined 105 cases of undoubted tertiary syphilis with the luetin test in addition to the routine tests. Of 54 patients with cutaneous, osseous, aortic, and neurologic disease, 48 gave at least one positive serological reaction, but only sixteen gave a positive luetin reaction, one of these occurring in a case of osseous syphilis in whom the other tests were negative. Of eighteen patients with interstitial keratitis, however, which has a demonstrable allergic element in the pathogenesis, all gave positive T.P.I. reactions and eleven (65 per cent.) gave a positive reaction to luetin. It would appear that the luetin test is even less dependable than the more usual routine examinations, but might possibly have a place as an additional test when the results of all other investigations are negative.

*Allene Scott*

**Treponemal Immobilization (Nelson) Test in Congenital Syphilis.** (Le test d’immobilisation des tréponèmes pâles (test de Nelson) dans la syphilis congénitale.)


The author, writing from the University Clinic of Dermato-Venereology, Lausanne, points out that a definite diagnosis of congenital syphilis is difficult when the clinical signs in the newborn infant, the results of standard serological tests for syphilis (S.T.S.), and the parental case history are not in agreement. The present study was designed to assess the value of the treponemal immobilization (T.P.I.) test in 51 cases (which are tabulated and briefly summarized) in which such disagreement existed. The test did not give a clear lead as to how to interpret the conflicting data, for in apparently identical circumstances it gave different results. In a further study the sera from 24 cases of treated congenital syphilis were subjected to S.T.S. and the T.P.I. test. In 22 of these the latter gave a positive result, whereas the S.T.S. were positive in twelve, negative in seven, and “dissociated” in three. In one of the two remaining cases the T.P.I. test gradually became negative 20 years after five courses of treatment, while in the other it first was negative, then gave a doubtful response (38 per cent. immobilization), and finally became negative without further treatment.

In the discussion a case is described in which positive results by both S.T.S. and the T.P.I. test were obtained with the cord blood at birth and again 18 days later in a newborn infant. Two months later, however, after 3 mega units penicillin had been given, all the reactions were negative. The author suggests that most probably the positive reactions in this case were due to transplacentally transmitted antibodies, so that a positive result in the T.P.I. test need not necessarily imply congenital syphilis. On the other hand transplacental infection late in pregnancy may produce a negative T.P.I. response soon after birth, but later a positive response during the first year of life. Alternatively, as in a further case described, the antibody titre may be too low to give a positive test; in this case “reactivation” by means of a dose of penicillin then produced a transitory positive T.P.I. test result.

It is concluded that in congenital syphilis a persistently negative response in the T.P.I. test is in favour of cure, but a positive test does not necessarily mean persistent infection.

*F. Hillman*


The antigen used in the fluorescent treponemal antibody test described by Deacon and others (*Proc. Soc. exp. Biol. (N. Y.)*, 1957, 96, 477; *Abstr. Wild Med.*, 1958, 24, 26) was a suspension of the virulent Nichols strain of *Treponema pallidum*. This paper from the New York State Department of Health, Albany, describes the results given by the same technique but using a suspension of the easily cultivable Reiter treponeme as antigen. The organisms were grown in thioglycolate broth with 10 per cent. heated rabbit serum, cultures being suitable for use from the 2nd to the 5th day after inoculation. When ready, 2 ml. of the undisturbed upper layer of the culture was added to 2 ml. of 0-002 per cent. sodium hypochlorite in saline, centrifuged after gentle mixing, washed in saline, and resuspended in enough saline solution to give a density of ten to fifteen treponemes per high dry microscopical field. This procedure prevented clumping of the organisms and changes in their morphology. The technique in all other respects followed Deacon’s except that the sera were tested at a dilution of 1 in 200.

Parallel tests performed with the Reiter and the Nichols strains of *T. pallidum* as antigen showed that sera from 103 healthy persons gave negative results with both antigens. A second group of 38 sera tested came from patients with non-treponemal conditions, 35 of whose sera had given positive reactions with cardiolipin antigens; these responses were thought to be non-specific because all the patients gave a negative response in the treponemal immobilization test. In this group the fluorescent test with Nichols treponemes was negative in all cases, but that using Reiter organisms was positive in one. Quantitative tests on sera from 51 syphilitic patients showed that the Reiter antigen gave a titre double that obtained with the Nichols antigen in 16 instances, while it was half as high in five sera, the titres being approximately the same in the remaining patients. This suggests that the Reiter treponeme is slightly though significantly more sensitive as an antigen for detecting syphilitic antibody.

The authors consider that, although further evaluation will be necessary, the Reiter treponeme (which is easily cultivated in vitro) may be a possible substitute for the
virulent Nichols organism (which can only be cultivated in vivo) in the fluorescent treponemal antibody test and that this would facilitate the use of the test in diagnostic laboratories.

A. E. Wilkinson


GONORRHOEA


Streptomycin has largely been used as the drug of first choice for the treatment of gonorrhoea in France since 1951, mainly from the fear that penicillin might mask a concomitant infection with syphilis. However, the diminishing effectiveness of streptomycin led to the present studies, which were carried out at the Institut Alfred Fournier, Paris. Sensitivity tests were performed by inoculating 25 × 10^6 gonococci on to horse plasma agar plates in which various graded concentrations of the antibiotics studied were incorporated. Results were read after 48 hours' incubation, complete inhibition of growth being taken as the end-point.

Streptomycin. Of 341 strains of gonococci tested, 68·9 per cent. were inhibited by a concentration of 10 μg per ml. or less and 7·6 per cent. by 30 μg per ml., while 22·9 per cent. grew in a concentration of 1,000 μg per ml.

Penicillin. Of 327 strains tested, 72·5 per cent. were inhibited by 0·05 unit per ml. or less, but 26·6 per cent. required 0·1 to 1·0 unit per ml. for complete inhibition and three strains (0·9 per cent.) were found resistant to 1·0 unit or more per ml. [The actual concentration inhibiting these three strains is not stated.] Of the strains which had proved completely resistant to streptomycin, 76 were re-tested against penicillin, when 44 of them were found to be sensitive to the latter. Although no true cross-resistance between the two antibiotics was found, strains selected on a basis of streptomycin resistance tended to have lower sensitivity to penicillin than unselected strains.

Tetracycline. The 62 strains tested with this antibiotic were all found to be sensitive, as were 61 strains tested with spiramycin. Only ten out of 154 strains of gonococci showed resistance to sulpha-hiazole.

In 1957 the usual treatment of gonorrhoea in France comprised two injections of 1 g. dihydrostreptomycin given 4 to 6 hours apart; with this dosage the failure rate was 9·8 per cent. in a series of 3,119 cases treated. In the first 10 months of 1958 (2,471 cases), the failure rate was 13·6 per cent. Because of the rising failure rate the same dosage of streptomycin was then combined with a course of 20 g. sulpha-hiazole given over 5 days. The failure rate thereupon fell to 8·2 per cent. but rose progressively to 12·9 per cent. by September, 1960. Sensitivity tests on gonococci isolated from 242 patients treated with streptomycin alone showed that there was almost complete correlation between the carriage of streptomycin-resistant strains and clinical failure to respond to this treatment. Patients who failed to respond to streptomycin were re-treated with 600,000 units of aqueous penicillin together with 4 ml. of a broth vaccine (‘propidion’). The proportion of such patients who failed to respond to this treatment was 9·2 per cent. in 1958, 11·6 per cent. in 1959, and 15·6 per cent. in the first 9 months of 1960. The authors envisage that in the future treatment of gonorrhoea streptomycin may have to be abandoned or at least reinforced with other anti-gonococcal agents, a situation which will entail some serious practical problems.

A. E. Wilkinson


This paper from the Venereal Disease Research Laboratory, U.S. Public Health Service, Chamblee
Georgia, and Fulton County Health Department, Atlanta, Georgia, describes the use of the fluorescent antibody method in the diagnosis of asymptomatic gonorrhoea in women. The subjects of the study were 213 women who were examined shortly after admission to prison, were free from symptoms or signs of gonorrhoea, and had not been named as sexual contacts of men suffering from the disease. Specimens from the urethra, cervix, and vagina were examined in each case using the delayed fluorescent antibody method (Deacon and others, Publ. Hlth Rep. (Wash.), 1960, 75, 125; Abstr. Wild Med, 1960, 28, 192) for the detection of Neisseria gonorrhoeae. Of 162 Negro and 51 white women, 34 (20-9 per cent.) and ten (19-6 per cent.) respectively were found to be harbouring gonococci. Thus gonorrhoea was diagnosed in 44 (20-6 per cent.) of the 213 women examined. Of 74 women who were re-examined after one week during which no treatment was given three tests were negative on both occasions in 51, positive on both in thirteen, positive on the first occasion and negative on the second in six, and negative on the first and positive on the second in four.

The authors conclude that relatively large numbers of women harbour N. gonorrhoeae without signs or symptoms and that the fluorescent antibody technique is a rapid and effective diagnostic method in such cases. Prisons may be a fruitful source of asymptomatic carriers of gonococci. [Keighley (Lancet, 1960, 2, 253; Abstr. Wild Med, 1961, 29, 13) reported that 48-9 per cent. of girls between 15 and 20 years of age examined in Holloway Prison were suffering from gonorrhoea as diagnosed by ordinary methods.] The effectiveness of any laboratory method depends upon the specimens obtained by the examining physician being adequate. Multiple sites should be tested, and re-examination may be expected to lead to the detection of additional cases of infection.

[The importance of the latency of gonorrhoea in women is stressed once again. Rectal infection is frequently asymptomatic, and it is likely that the number of positive findings would have been increased if that site had been tested also. The fluorescent antibody method is obviously a valuable diagnostic procedure, but further information is required to compare the results obtained by it with those obtained by the use of Stuart’s transport medium and the immediate examination of stained smears.] Eric Dunlop


It is pointed out that, while a single intramuscular injection of penicillin remains the treatment of choice for acute gonorrhea, in patients who are allergic to penicillin other antibiotics must be given, preferably in a single dose since clinic patients cannot be relied upon to attend for repeat injections.

The rate of renal clearance of demethylchlorotetracycline is much slower than that of tetracycline and after a single oral dose of the former there is an effective serum level of the drug for a comparatively long time. Of 132 strains of Neisseria gonorrhoeae tested for susceptibility in vitro, 88 per cent were equally or more sensitive to this antibiotic than to three other tetracycline derivatives.

A single oral dose of 0·9 g. demethylchlorotetracycline was given to 43 male patients with acute gonococcal urethritis at Massachusetts Memorial Hospitals, Boston. The diagnosis was confirmed by the finding of Gram-negative diplococci in stained smears and culture of N. gonorrhoeae from urine sediment. The patients were seen each week for 3 weeks, urine being cultured at each visit. Of the 43 patients, 36 returned for follow-up, but of these, fourteen returned once, fifteen twice, and only seven returned three times. Of the 36 patients followed up, 32 were classified as cured; the remaining four patients, in whom treatment failed, had positive cultures and responded to penicillin. Toxic effects, mainly nausea and vomiting, were observed in six patients successfully treated. It is considered that a smaller, less toxic, single dose might be equally effective in future treatment.

A. J. Gill


This paper from the State Serum Institute, Copenhagen, represents an extension of work on the sensitivity of Neisseria gonorrhoeae previously reported by the authors (Brit. J, vener. Dis., 1958, 34, 227; Abstr. Wild Med., 1959, 26, 80). The medium used for the sensitivity tests was a chocolate agar base with 30 per cent. ascitic fluid in which antibiotics were either incorporated in graded amounts (the dilution method) or were applied as tablets containing 15 μg. crystalline benzylpenicillin, 3 mg. streptomycin, or 1 mg. tetracycline (the disk method). In the former, strains were classed as sensitive if they showed 50 per cent. inhibition of growth at 0·035 μg. of penicillin per ml., 3·7 μg. of streptomycin per ml., or 0·6 μg. of tetracycline per ml. In the disk test strains were designated sensitive if they showed inhibition zones 35 mm. or more in diameter with penicillin or 36 mm. or more with the other two antibiotics.

Penicillin sensitivity tests were performed on 210 strains of gonococci isolated in 1957 and 250 in 1958. [These strains were partly selected in that they came from patients in whom treatment had been unsatisfactory.] In each year 39 per cent. of the strains showed a reduced sensitivity to penicillin and it was noted that the proportion of the most sensitive strains had fallen from 22·4 per cent. in 1957 to 12·8 per cent. in 1958. Tests for streptomycin sensitivity were requested in respect of 45 strains isolated in 1957 and 26 (65·4 per cent.) of these showed diminished sensitivity. In 1958 tests against streptomycin were performed on the 250 strains which had been tested with penicillin and 58·2 per cent. showed a lessened sensitivity to the former antibiotic; only two strains were found to be completely resistant to streptomycin and these both came from the same patient. It was noted that strains which were less sensitive to penicillin also tended to be less sensitive to streptomycin.

In June, 1957, there was a sudden increase in the number of strains isolated which showed only scanty growth.
on chocolate agar and fermented glucose poorly or not at all. By January, 1958, such atypical strains accounted for about 40 per cent. of all isolations received from all parts of Denmark. Serological tests on fifty of these strains showed that they were true gonococci despite their abnormal properties. Lyophilized strains which had been isolated in 1944 grew well on the medium then in use and showed normal fermentation characteristics, so that the alterations noted in 1957–8 were thought to be due to strain peculiarities rather than to deficiencies in the culture media. The atypical strains tended to be more sensitive to both penicillin and streptomycin than were typical strains selected from routine diagnostic cultures made in 1957, although sensitivity studies were difficult to perform because of the paucity of growth. The broth used in the basal medium had been made from ox or veal meat; the use of broth made from ox heart muscle resulted in considerably larger colonies and more distinct fermentation reactions, while a broth made from human placenta proved even more satisfactory. It is suggested that the appearance of these atypical strains of gonococci may have been due to penicillin therapy.

The stability of the sensitivity of gonococci to antibiotics was examined by subculturing twenty strains showing reduced sensitivity to penicillin on penicillin-free medium daily for 30 to 90 days and then comparing their sensitivity with the same strains which had been lyophilized. The subcultured strains tended to show larger inhibition zones in disk tests with streptomycin and tetracycline, but this may possibly have been due to changed growth requirements rather than to increased sensitivity. Tests against penicillin by the dilution method showed no significant differences between the subcultured and lyophilized strains. A stock strain which was relatively insensitive to penicillin kept its original level of sensitivity despite frequent subculture for over 2 years.

A. E. Wilkinson


**NON-GONOCOCCAL URETHRITIS AND ALLIED CONDITIONS**


The acute arthritis which is an outstanding feature of Reiter’s disease and thus suggests some resemblance to rheumatic fever has prompted several investigators to search for cardiac lesions. In this paper the authors describe, from St. Mary’s Hospital, London, three cases of Reiter’s disease, all in males, in which aortic incompetence subsequently developed.

The first patient, a West Indian, having at the age of 29 contracted gonorrhoea, had his first attack of Reiter’s disease at the age of 38, when he developed pericarditis and a harsh apical systolic murmur, the electrocardiogram (ECG) showing a prolonged P–R interval of 0.28 second. When he was seen 4 years later there was evidence of aortic incompetence, the patient having, in the intervening period, had several attacks of polyarthritis (one of which was treated by corticosteroids) and one of gonorrhoea; the latter had responded to penicillin, but was followed by a further attack of non-specific urethritis.

The second patient also developed Reiter’s disease after contracting gonorrhoea, in 1940, at the age of 27. When examined in 1959, having then been suffering from dyspnoea of effort for about one year, he was found to have aortic incompetence. The ECG showed the P–R interval to be 0.28 second.

The third patient developed Reiter’s disease 8 years after an attack (in 1927) of gonorrhoea, which was followed by recurrent attacks of iritis. In 1957, when he was 53, he was found to have aortic incompetence, the P–R interval being 0.24 second. He was observed for a further 3 years, during which time he has had two further attacks of iritis, but his cardiac condition remains unchanged.

The authors also describe the case of a woman aged 50 who died in cardiac failure due to aortic incompetence which had been first diagnosed 5 years previously. This patient had had transient arthritis, iritis, and cervicitis, but the diagnosis of Reiter’s disease could not be definitely established. Post mortem examination revealed atheroma and thickening of the intima of the aorta and thickening of the adventitia with endarteritis. changes which are
usually ascribed to the late effects of syphilis and rheumatic endocarditis. (The three male patients described were discovered as a result of a long-term study of 215 cases of Reiter’s disease.)

H. F. Reichenfeld


Work at the Institute of Ophthalmology, London, shows that many male patients with uveitis have a chronic genito-urinary infection, with sacro-iliac arthritis, ankylosing spondylitis, and Reiter’s disease. No common causative organism has been discovered. A. G. Cross


An epidemiological study of the disease in Algeria proves that it affects the young metropolitan soldiers during the first summer of their stay; it is endemically sporadic and begins with diarrhoea. It seems to be due to a virus of the enterovirus group. Cortisone is effective except in severe cases where gold salts seem to give good results.

S. Vallon


CHEMOTHERAPY


The results of laboratory studies of methicillin and of administration of the drug in staphylococcal infections are described in this paper from Lancaster Hospital, Lancaster, New Brunswick, Canada. A total of 35 strains of coagulase-positive staphylococci isolated from patients were tested for their sensitivity to benzylpenicillin, phenethicillin, and methicillin by the tube dilution method.

All strains were sensitive to methicillin in a concentration of 0.39 to 3.12 µg. per ml., the majority being sensitive to 1-56 µg. per ml. The degree of sensitivity of the strains most sensitive to benzylpenicillin was less than that to methicillin and this sensitivity was not changed by the size of the inoculum, whereas with benzylpenicillin a large inoculum caused an increased degree of resistance to all penicillinase-producing organisms. Phenethicillin occupied an intermediate position, only the heavy penicillinase producers being affected by the size of the inoculum. Phage-typing of ten strains of staphylococci from twelve patients showed that they belonged to phage Groups 1, 2, and 3 and included Strains 80, 81, and 82. When the organisms were tested by the tube dilution method for sensitivity to benzylpenicillin and methicillin it was found that the strains were uniformly sensitive to 0.78 to 1.56 µg. methicillin.

Methicillin was given to twelve patients infected with coagulase-positive staphylococci (nine resistant and three sensitive strains to benzylpenicillin). The criteria for assessing the response to the drug were a fall in temperature or a fall in the erythrocyte sedimentation rate, a change in the leucocyte count and differential shift, a change in the character of the sputum or exudate, negative findings on bacteriological culture, and radiological and clinical improvement. The drug was given in a dosage of 0.5 to 1 g. every 4 to 6 hours for 7 days, by intramuscular injection in eleven cases and intravenous injection in one. Blood samples for drug assay were taken at the time the first dose was given and again after 1, 2, and 4 hours. On the third day of treatment a 24-hour sample of urine was collected for assay; renal toxicity was assessed biochemically.

Of the twelve patients, ten recovered completely after treatment with methicillin, including four suffering from staphylococcal pneumonia (one of whom had had a previous course of antibiotic therapy and one who was sensitive to penicillin 2 years previously but showed no reaction to methicillin), four patients with boils, one with wound infection, and one with penile discharge. There was only temporary improvement in one patient who had had extensive treatment with various antibiotics for staphylococcal osteomyelitis, and in one elderly patient with dermatitis herpetiformis and boils there was a relapse 6 days after the drug was discontinued.

Determination of blood levels of penicillin [form of penicillin not stated] in six cases showed that, with a dosage of 0.5 g. every 4 hours, a peak blood level of 10 to 12 µg. per ml. was reached in one hour and therapeutic levels were still in evidence at 3 hours. Intravenous injection was followed by higher initial blood levels than intramuscular injection, but the initial blood level was better sustained when the drug was given intramuscularly. Assay of the urine indicated that the greater part of the drug was excreted rather rapidly through the kidneys.

Anne Tothill


This work was carried out on behalf of the Czechoslovak Experimental Institute for Antibiotics to investigate the blood levels attained in children after the oral administration of phenoxymethylpenicillin (penicillin V) of Czech manufacture. The authors state that no previous work of this nature has been undertaken to determine
the optimum dosage of this antibiotic in children, and they consider that the dosage usually recommended is in some cases rather higher than necessary to achieve satisfactory clinical results. Workers at the Experimental Institute for Antibiotics found that the blood levels attained in adults did not differ whether phenoxymethylpenicillin itself or its potassium salt was used. On the other hand it has been reported from the U.S.A. that when the potassium salt is given the blood level reached is 50 to 100 per cent. higher than when phenoxymethylpenicillin is given. It is also stated that even higher blood levels can be obtained if ascorbic acid is given simultaneously.

Blood levels were estimated by a modification of the Hildick–Fellow-Smith micro-method, blood samples being taken in one group 1, 3, 5, and 7 hours after administration of the dose and in a second group after 1, 2, 4, 6, and 8 hours. A total of fifty series of blood-level estimations were carried out on thirty babies and twenty older children, the dose of both phenoxymethylpenicillin and its potassium salt being 100,000 units for infants and 200,000 units for older children. The authors show the results of their investigations in four tables and draw the following conclusions.

1. The maximum blood level of penicillin in babies and children was reached 3 hours after the ingestion of 100,000 units and one hour after the ingestion of 200,000 units of phenoxymethyl penicillin.

2. The blood concentration reached in all groups was higher than the levels previously mentioned in the literature.

3. In all fifty cases the penicillin in the blood was still at an active level 6 hours after administration, while in the thirty infants observed active levels were maintained for as long as 7 hours.

4. Comparison of the two preparations showed that the potassium salt produced somewhat higher levels after 6 hours than the free acid.

5. The higher blood levels of penicillin noted in these children may have been partly due to the simultaneous administration of ascorbic acid.

6. Potassium phenoxyethylpenicillin is to be preferred to other preparations of penicillin, including those given by injection, since effective blood levels are reached in a shorter time and are maintained for longer periods after its administration.

Paul Frankl


Two crossover experiments and one Latin Square experiment were performed to examine the penicillin serum concentrations obtained following the oral administration (fasting) of 250 mg. potassium penicillin, the intramuscular injection of 250 mg. potassium penicillin G, and the intramuscular injection of 250 mg. of potassium phenethicillin.

The average penicillin serum concentrations obtained were essentially the same for all three formulations. The areas under the linear curves portraying these levels were statistically the same, confirming the similarity of total absorption among the three formulations. On the basis of three separate experiments, it appears that the same penicillin serum concentrations can be obtained with 250 mg. potassium phenethicillin administered orally (fasting) as with 250 mg. potassium penicillin G administered intramuscularly. —Author's summary.


It is pointed out that more than a quarter of a million patients are treated with penicillin each year in venereal disease (V.D.) clinics in the United States and that although other antibiotics are therapeutically effective, none is a fully adequate substitute for penicillin and all are more costly. The incidence of reactions, particularly of severe reactions, and the deaths attributable to penicillin are therefore matters of concern to public health authorities. In this investigation reported from the Public Health Service, Atlanta, Georgia, the Health Departments of 21 States, the District of Columbia, and Puerto Rico and five border reception centres cooperated with the object of determining the types and frequency of such reactions. Each clinic supplied data concerning patients treated during a 3-month period and since the periods of investigation did not coincide at all centres the collection of records extended from March, 1959, to March, 1960. The reactions were divided into three classes—anaphylaxis, serum sickness, and urticaria—and in most cases anaphylactic reactions were classified as "mild" or "moderate to severe".

During the period of study 35,550 patients were treated with penicillin, 25,550 in V.D. clinics and 9,946 at border reception centres. Reactions occurred in 255 cases or 7·2 per 1,000 patients treated; in V.D. clinics the incidence was 9·7 per 1,000 patients treated. Urticaria was the most frequent reaction, occurring in 5·7 per 1,000. Anaphylaxis was recorded in 27 cases or 1·1 per 1,000, but in only nine instances was it classified as "moderate to severe". Serum sickness occurred in eleven cases. At the border reception centres the incidence of reactions was less than 1 per 1,000 patients treated, the principal reaction being syncope, which was caused by fear of the needle as readily as by penicillin. Patients attending the reception centres were Mexican male labourers who were physically fit for strenuous labour and, because of circumstances in the country of their origin, had received little or no treatment with penicillin in the past. It was also likely that they might not report delayed reactions for fear of rejection for proposed employment. Because of these factors the authors' further analysis was confined to data from the V.D. clinics.

There was considerable variation in the reports from the clinics, the number of reactions varying from 0 to more than 25 per 1,000 patients treated. In general, the larger the quantity of penicillin prescribed and the longer the duration of treatment, the greater the number of reactions reported. In patients receiving a single session of treatment the incidence of reactions was...
approximately the same for schedules of less than 1,200,000 units as for schedules of 1,200,000 to 2,300,000 units; however, the rate almost doubled for schedules of 2,400,000 to 4,700,000 units. In patients given treatment for 2 to 7 days the incidence of reactions varied from 8·4 per 1,000 patients treated with 1,200,000 to 2,300,000 units to 38 per 1,000 with 4,800,000 to 7,100,000 units. Correspondingly large increases in reaction rates were observed with increased dosage for 8 or more days. Reactions were fewer after single than after multiple injections; therefore if the total dosage was low there were fewer reactions with repository preparations such as procaine benzylpenicillin in oil with 2 per cent. aluminium monostearate and benzathine penicillin than there were with crystalline penicillin. With schedules in which larger doses and therefore more injections were given no significant differences related to the type of penicillin were observed. The reaction rates were much the same for patients who had no history of past treatment with penicillin and for those who had had penicillin previously without ill effects. This was thought to be due to exposure of patients to penicillin for minor illness or through dairy produce and other foods without their knowledge—an exposure regarded as almost universal in the United States. Negroes were less prone to reactions than white subjects. The incidence of reactions was much the same in white males as in white females, but was significantly higher in negroes than in negroes.

The reaction rates in patients with gonorrhoea and the contacts of such patients were approximately the same—namely, 7·1 and 6·5 per 1,000 respectively. Both values were significantly lower than the reaction rate for syphilis of 19·7 per 1,000, a disparity which was still present when comparison was limited to those patients treated with 2,400,000 units administered on one occasion. A possible explanation was that patients were observed more closely after treatment for syphilis.

When the findings were compared with those of a similar study carried out in 1954 it was seen that in the earlier year reactions to penicillin occurred in 5·95 per 1,000 patients treated compared with 9·71 per 1,000 in 1959. It seemed likely that the general increase in dosage of penicillin for gonorrhoea in later years was partially responsible for this difference. Only one death occurred among more than 100,000 patients treated at the participating clinics during the year in which these records were collected.

A. J. King


Furaltadone was given to forty patients at Hammersmith Hospital, London, in the treatment of wound infection or respiratory- or urinary-tract infection following operation. It was given in a dosage of 250 mg. four times a day with meals or in a glass of milk. Bacteriological studies and sensitivity tests against furaltadone and other chemotherapeutic agents were carried out. The blood level of furaltadone in nine patients 5 hours after an initial dose of 500 mg. averaged 3·1 ug. per ml. Infections due to Staphylococcus pyogenes, Escherichia coli, Streptococcus faecalis, Diplococcus pneumoniae, and Haemophilus influenzae responded to this drug, but not infections which were due to Pseudomonas pyocyanea or B. proteus.

With the exception of gastrointestinal disturbances there were no toxic manifestations. I. Ansell


PUBLIC HEALTH AND SOCIAL ASPECTS


That the prostitute is but one factor in the spread of venereal disease is indicated. The prostitute, especially the itinerant male, is equally important. Evidence is given to show that itinerant males are more prone to venereal disease than non-itinerants, and that they frequently contract such diseases from prostitutes. The itinerant male usually contracts his disease from the static female. Figures are presented which indicate that over 90 per cent. of the inmates of brothels in many countries of the world are nationals of the country in which the brothels are situated. The tendency is noted for more studies to be undertaken of the prostitute as opposed to the prostitute. Prostitution flourishes in situations of political and economic confusion and obeys the law of "supply and demand".

The risk of an individual contracting venereal disease from a prostitute is considered. Some of the data presented indicate that the risk is lower than might be expected. The role of alcohol in the spread of venereal disease is discussed. The association is not necessarily so simple as it first appears, for the effect of alcohol on the causation of venereal diseases seems to be more indirect than direct. Alcohol may encourage prostitution and contrariwise prostitution may boost the sales of alcohol.—[Author's summary.]


MISCELLANEOUS


