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.

SYMPHILIS (Clinical)


During the past 10 years, 194 patients with general paralysis of the insane were admitted to the Neuro-psychiatric Branch of the Novi Sad District Hospital, Yugoslavia. These patients constituted 5-4 per cent. of all first admissions during this period, indicating that in Yugoslavia general paralysis is less of a rarity than it has become in other countries. The illness was of gradual onset in 132 cases and of sudden onset in 64. The predominant symptoms at the time of admission were those of simple dementia in 89 cases, confusion in 34, euphoric dementia in 21, depressive state in twenty, expansive syndrome in fifteen, paranoid state in six, and various other conditions in nineteen. The authors point out that the clinical picture appears to have changed in that the classic syndrome of delusions of grandeur has become considerably less frequent than in the past, the expectation of life has markedly increased, and the severe dementias are much rarer. They believe that these changes are due to the influence of the changed socio-economic milieu on the form of the disease and to the occurrence of a higher proportion of cases of cerebral syphilis with a predominantly meningovascular as opposed to a predominantly parenchymatous reaction. J. Hoenig


The relevant literature is reviewed and the authors report their own experience in a series of 137 patients with endemic syphilis in Syria. No clinical evidence of neurosyphilis was found and the cerebrospinal fluid (C.S.F.) was normal in all patients except one in whom a weakly positive V.D.R.L. reaction was thought to be due to passive transfer of reagin from the blood to the C.S.F. The mechanism of the apparent immunity of the central nervous system in endemic syphilis is not known, but it is suggested that it may be due to the repeated superinfections known to occur in populations living in hyperendemic areas. It is also pointed out that cutaneous relapses are not seen in the course of endemic syphilis in contrast to venereal syphilis and that this difference indicates a different level of immunity in the two forms of syphilis. G. W. Csonka


SYMPHILIS (Serology)


This paper from the Institut Alfred Fournier Paris, reports a comparison of the results given by the fluorescent treponemal antibody (F.T.A.) test, the treponemal immobilization (T.P.I.) test, and a battery of standard tests for syphilis (S.T.S.), comprising the Kolmer W.R. with heart extract and cardiolipin antigens, and the Kahn, Kline, and Reiter tests, which were performed on 1,171 sera and 126 samples of cerebrospinal fluid (C.S.F.). The F.T.A. technique was based on that of Deacon and others (Proc. Soc. exp. Biol. (N.Y.), 1957, 96, 477; Abstr. Wild Med., 1958, 24, 26). Sera were tested at dilutions of 1:100 and 1:200 and C.S.F. either undiluted or diluted 1:10, 0-05 ml. being allowed to act on the treponemes for 30 minutes. After washing, 0-05 ml. of a commercially
available goat antihuman globulin conjugate diluted to its optimum titre was applied for 30 minutes. Deacon’s criteria of reactivity were followed.

The specificity of the T.F.A. test was assessed by testing 465 normal sera which had given negative results with the T.P.I. test and the S.T.S.; these were all found to be non-reactive in the F.T.A. test. Sera from a further twelve patients were thought to have given non-specific reactions with the S.T.S. because the T.P.I. and Reiter tests were negative; these also gave negative results in the F.T.A. test. Complete agreement was found between the F.T.A. and T.P.I. tests on 616 sera which were T.P.I.-positive and most of which gave positive results with lipoidal antigen tests. Quantitative F.T.A. tests were then performed on 78 sera from known cases of syphilis; the results suggested that the F.T.A. test became positive earlier than the other tests, and in four cases of dark-field positive primary syphilis it was the only test to give a positive result. Maximum titres were found in secondary syphilis; the titres tended to be lower in treated cases and in late syphilis. The F.T.A. test thus appeared to be more sensitive than the lipidial antigen tests.

All of 67 specimens of C.S.F. from non-syphilitic patients gave a negative result by the F.T.A. test, as did also six specimens from syphilitic patients without evidence of involvement of the central nervous system. Samples of C.S.F. from 53 patients with various types of neuro-syphilis all gave a positive result in the F.T.A. test, the highest titres being observed in patients with general paresis.

The authors suggest that the antibody detected by the F.T.A. test may differ from immobilizing antibody, basing this suggestion on the high sensitivity of the test in early syphilis, whereas immobilizing antibody usually first becomes demonstrable relatively late in the primary stage. In contrast, in late syphilis, the titre in the T.P.I. test is said to be higher than that of the F.T.A. test. They conclude that it seems unlikely that the F.T.A. test will be of help in differentiating between the individual treponematoses, since fluorescence tests using Treponema pallidum, T. pertenue, and T. cuniculi as antigens all gave similar negative or positive results with normal and syphilitic sera.

**ABSTRACTS**


The fluorescent treponemal antibody (F.T.A.) test was performed on sera sent to the Walter Reed Army Medical Center, Washington, D.C., for examination by the treponemal immobilization (T.P.I.) test; the first technique described by Deacon and others (*Proc. Soc. exp. Biol. (N.Y.),* 1957, 96, 477; *Abstr. Wild Med.*, 1958, 24, 26) was used, but the sera were incubated at room temperature instead of at 37°C. However, when the recommended serum dilution of 1 in 5 was used it was found difficult to differentiate moderately reactive from non-reactive sera owing to non-specific fluorescence. The authors therefore modified the procedure, first by rinsing the slides free from excess serum and antihuman globulin conjugate on a mechanical rotator, and later by testing sera at a dilution of 1 in 100. In 745 sera tested by the original method modified as described 90 per cent. agreement was obtained between the results of the F.T.A. and T.P.I. tests, 6 per cent. of the sera being reactive only with the F.T.A. test and 4 per cent. only with the T.P.I. test. Repeated tests on sera which gave discrepant results by the two procedures suggested that reproducibility was better with the F.T.A. than with the T.P.I. test.

It is possible that the result of the F.T.A. test may be affected by sensitization of the treponemes in vivo by antibody produced in the source animal (the rabbit) and therefore one of the essentials of the test is that the organisms should be harvested from the testes not more than 24 hours after the appearance of definite orchitis. To confirm this, F.T.A. tests were performed using as antigen a treponeme suspension obtained 7 days after the development of orchitis in the rabbit; this showed marked “sensitization” of the organisms and greatly reduced their activity with human syphilitic antibody, the reduction in titre being 8-fold compared with the titre obtained with an unsensitized suspension. This suggested that the sensitization of the treponemes by the rabbit antibody had exercised a blocking effect and prevented union with the antibody.

The authors consider that their results indicate that the F.T.A. test is more sensitive than, and at least as specific as, the T.P.I. test and relatively simple to perform. They find it a valuable adjunct to the latter, particularly when examining sera with threshold amounts of antibody or those showing non-specific immobilization which prevents a valid T.P.I. result being obtained.

**A. E. Wilkinson**


It has been reported that *Treponema pallidum* when freshly isolated from syphilitic lesions does not show reactivity with syphilitic sera in agglutination or immobilization tests; the organism becomes reactive only after incubation *in vitro*. This initial non-reactivity has been attributed to the presence of a non-antigenic capsule or slime layer on the organism. Histological studies of the mucoid material found in the early skin lesions of syphilis in rabbits have suggested that the capsular material may be similar to hyaluronic acid.

The effect of the enzymes hyaluronidase and lysozyme on the rate of immobilization of *T. pallidum* by syphilitic serum in the presence of complement was studied at Johns Hopkins University, Baltimore. Treponemes were incubated with 100 to 400 μg. bovine testicular hyaluronidase per ml. of suspension for up to 10 hours before the addition of syphilitic serum and complement; no appreciable acceleration of immobilization occurred. This
suggested that hyaluronidase was not the enzyme responsible for the development of the reactive state of treponemes. Lysozyme was found to have a very marked effect in accelerating immobilization. In the presence of 100 µg. lysozyme per ml., a syphilitic serum immobilized 50 per cent. of the treponemes in 4 hours; without the enzyme this did not occur until the mixtures had been incubated for 10 hours. Treponemal immobilization (T.P.I.) tests are usually read after 18 hours' incubation at 35° C.; it was found that the titre of immobilization reached at this time could be produced after only 10 hours with added lysozyme. In tests carried out on 46 non-syphilitic sera, there was no evidence of non-specific immobilization in the presence of 100 µg. lysozyme per ml., but when the lysozyme level was increased to 500 µg. per ml. the survival of the treponemes was appreciably reduced.

The authors consider that their results are consistent with the destruction of a non-antigenic mucoplycosaccharide surface layer of treponemes by lysozyme. They suggest that the effect of higher concentrations of complement in increasing the sensitivity of the T.P.I. test may be due to the excess lysozyme contributed by the extra guinea-pig serum.

A. E. Wilkinson


In a previous investigation carried out at the University Skin Clinic, Jena (Rietschel and Ettig, Derm. Wschr. 1961, 143, 241; Abstr. Wild Med., 1961, 30, 104) it was found that certain vulcanization accelerators used in the manufacture of rubber stoppers had a toxic effect on sera used in the treponemal immobilization (T.P.I.) test of Nelson. However, even after the substitution of cork for rubber it was noted that certain sera soon became toxic and it was decided to investigate the possibility that this was due to bacterial contamination.

In preliminary studies it was found that certain bacteria when added to serum had a detrimental effect on the test, whereas others had no such effect. In a systematic survey seven common bacterial species and seven species which were isolated from contaminated sera were added to T.P.I.-negative serum. It was found that even small additions of Staphylococcus aureus or Proteus vulgaris resulted in 100 per cent. non-specific immobilization. On the other hand, Bacillus mesentericus, Pseudomonas pyocyanea, and some of the unidentified contaminants had little effect on the T.P.I. test result. The addition of streptomycin to the serum in a concentration of 5 mg. per 0·5 ml. controlled contamination without adversely influencing the T.P.I. test and this practice has now been adopted as a routine measure.

G. W. Csonka


**SYphilis (Therapy)**


From the University Skin Clinic, Frankfurt on Main, the author describes the case of a patient with superficial trichophytin infection who was treated with griseofulvin. Since the appearance of this patient’s teeth aroused some suspicion of congenital syphilis serological tests were performed. The result of the treponemal immobilization test showed that treponemical substances were present in the serum. However, when this test was repeated 2 weeks after administration of griseofulvin had been stopped it had an entirely negative result. It was thought possible that griseofulvin might have been responsible for the treponemical effect observed and in view of the widespread use of this drug it was decided to investigate whether it had any effect on *Treponema pallidum in vivo* which could lead to the presence of syphilis being masked. To this end four patients with dark-field positive syphilitic lesions were given large doses of griseofulvin. It was found, however, that the drug had no influence on the recoverability of *T. pallidum* from the sores and did not promote healing of the syphilitic lesions.

G. W. Csonka


**Gonorrhoea**


Synnematin B, an antibiotic produced by the mould *Cephalosporium salmosynematum*, Strain 3590 A, and known to be somewhat related to penicillin, is treponemical and markedly lethal to *Neisseria*. It is not, however, readily available. The authors of this paper from the Detroit and Michigan Departments of Health describe a trial of Synnematin B on 132 males with proved (smear and culture) acute gonorrhoea. All the patients were given one intramuscular injection of 300,000 units of Synnematin B. There were frequent complaints of local pain but no allergic reactions. Within 30 days seventeen (13 per cent.) of the patients again had positive smears and cultures, but according to the criteria adopted only five (4 per cent.) were considered treatment failures, the others being considered to have a reinfection.

The results are compared with those in a random series of 100 similar patients treated with 1,200,000 units of penicillin. In this group eight patients had a recurrence within 30 days, but only one was considered a treatment failure. The authors state that Synnematin B appears to have great promise in the treatment of acute gonorrhoea.

*Leslie Watt*


From the public health point of view it is considered that before a drug can be considered suitable for the primary treatment of acute gonorrhoea in patients seen at venereal disease (V.D.) treatment centres the following criteria must be satisfied:

1. the drug must be effective in a single dose;
2. potent antibacterial levels in the serum must be rapidly achieved;
3. allergic reactions or serious side-effects must be minimal or absent.

At the V.D. Centre of the Richland County Health Department, South Carolina, demethylchlortetracycline hydrochloride was given in the primary treatment of 267 patients with acute gonorrhoea. Alternate patients were allotted to one of two treatment regimens and received either four or six capsules of the drug, each containing 150 mg., as a single oral dose, the capsules being swallowed under observation; no other treatment was given. Blood levels of demethylchlortetracycline were determined in eight patients in each treatment group at 48, 72, and 120 hours, and all patients were asked to return for examination after one week. Treatment was considered a failure when smears were positive on re-examination except in those cases in which there had been further contact with the original source of infection.

Of 110 patients given 600 mg. and re-examined, 92 (84 per cent.) responded well, and of 128 given 900 mg., 119 (93 per cent.) were considered to be cured. Toxic side-effects, which were encountered in about 20 per cent. of patients receiving the lower dose and in 40 per cent. of those receiving 900 mg., were mainly gastro-intestinal disturbances which were usually mild and of short duration. No instance of anaphylaxis or skin reaction was observed.

In view of the apparent increase in anaphylactoid reactions after penicillin and the emergence of strains of *Neisseria gonorrhoeae* which are resistant to that antibiotic, the author considers that “it might seem advantageous to avoid penicillin therapy whenever possible”. In his view demethylchlortetracycline is effective in the treatment of gonorrhoea and particularly valuable for use in V.D. treatment centres.

A. J. Gill

As a consequence of alarming reports of an increase in “penicillin-resistant gonorrhoea” received from U.S. Naval units stationed in the Mediterranean area it was decided to investigate all cases of acute urethritis seen at the U.S. Navy Station Hospital, Naples, between October, 1960, and March, 1961. Of 42 such patients, 37 were found to have intra- and extra-cellular Gram-negative diplococci in the urethral discharge, which was purulent, and of these the discharge from 34 patients grew colonies resembling those of *Neisseria gonorrhoeae*. After subculture further identification in carbohydrate fermentation media showed that twelve of these patients were infected with *N. gonorrhoeae* and 22 with organisms of the *Mimeae* species. (*Mimeae* were first isolated by DeBord from the genital and conjunctival tract in 1939 and were so named by him because of their ability to mimic *Neisseria* in morphology, staining reactions, and culture characteristics; however, they do not produce acid in glucose solution.) Antibiotic sensitivity tests showed that all strains of *N. gonorrhoeae* isolated were sensitive to penicillin whereas most of the strains of *Mimeae* were penicillin-resistant. Clinically, the patients with *N. gonorrhoeae* infection responded readily to penicillin, but only four of the 22 patients infected with *Mimeae* did so satisfactorily, the remaining eighteen subsequently responding to broad-spectrum antibiotics. This study thus does not support the concept of penicillin-resistant *N. gonorrhoeae* infection.

This is an interesting paper, which suggests that identification of *N. gonorrhoeae* by smear alone may not be justified. It is a pity that the penicillin-resistant “*Mimeae*” are not more fully characterized, and in particular the results of serological studies and epidemiological investigations would have been of great interest. Further work into the nature of the *Mimeae* and their relationship to “gonorrhoea” is indicated.

G. W. Csonka


The authors of this report first review the incidence of gonococcal infection in Great Britain since 1946, and particularly since 1955, and then discuss the sensitivity of the organisms to penicillin alone and to penicillin in oil with 2 per cent. aluminum monostearate (P.A.M.). The investigation, the aim of which was to assess the pre-treatment sensitivity of gonococci and to determine the sensitivity of these organisms from patients who had failed to respond to treatment, included only patients attending venereal disease clinics, and nine large laboratories participated in the study. The culture media used and the methods for assaying sensitivity in vitro are adequately outlined. Although identical techniques were not used at the various participating centres, suitable cross-checks were carried out to assure comparability of results.

The highest incidence of decreased sensitivity of gonococci to penicillin was observed in Sheffield and Wakefield and, for a part of the period, in one area in London. The survey covered the period August, 1959 to March, 1960, and a total of 1,984 strains were examined. Of 137 strains from patients who had not responded to treatment, 73 were inhibited in vitro by as little as 0.06 unit of penicillin per ml. or less, giving rise to the suspicion therefore that these were not cases of treatment failure but cases of reinfection. As reinfection during the first post-treatment week appeared to be unlikely, the results obtained with organisms persisting in spite of treatment or appearing in the first week after treatment were considered to be more significant. Of 38 such strains, 32 were sensitive only to 0.125 to 1.0 unit of penicillin per ml.; in these cases 1-2 mega units of P.A.M. had proved ineffective. During the period of the study certain changes in the penicillin sensitivity of gonococci were noted; thus in Southampton and Manchester there was a decrease in the proportion of relatively resistant strains, but an increase in Birmingham, Liverpool, Wakefield, and Sheffield.

The suitability of sulphonamides for the short-term treatment of gonorrhoea is briefly considered. It is suggested that streptomycin should not be relied upon as a long-term substitute for penicillin because of the tendency for resistant strains to emerge. The emergence of penicillin-resistant strains, it is thought, may be a consequence of the use of slow-release penicillin preparations, since these produce a prolonged but comparatively low concentration of the antibiotic in the blood.

F. Hillman


CHEMOTHERAPY


The authors report the results of microbiological studies of “penbritin” (B.R.L. 1341), a new penicillin prepared from 6-aminopenicillanic acid which is acid-stable, active against a wide range of Gram-positive and Gram-negative bacteria, and highly bactericidal. The compound is 6\([\text{D}(-)\text{oxygenopenylacetamido}\)] penicillanic acid and is sparingly soluble in water.

Studies in vitro showed that penbritin was only slightly less active against the pyogenic cocci than benzylpenicillin (G) and substantially more active than tetracycline and chloramphenicol. Against Gram-negative bacilli penbritin showed a range of activity generally similar to that of tetracycline. It was highly active against Haemophilus influenzae, Neisseria catarrhalis, and various members of the Salmonella group, but showed little activity against Aerobacter aerogenes and Pseudomonas pyocyanae. Some strains of Proteus which were sensitive to tetracycline were resistant to penbritin, but in 82 per cent. of 121 strains tested the minimum inhibitory concentration (M.I.C.) was 5 \(\mu\)g per ml. or less. Penbritin is not stable to penicillinase and therefore was not effective against penicillinase-producing organisms. The presence of serum had little effect on M.I.C. values, nor had the size of the inoculum in tests with Salm. typhi or Shigella sonnei. In most tests the pH had no significant effect on the activity of penbritin, but against two strains of Escherichia coli and one of Streptococcus faecalis the antibiotic was more active at a slightly acid pH than at higher pH values. Emergence of strains resistant to penbritin developed stepwise in the typical penicillin manner.

A. Ackroyd


In these pharmacological studies of the new broad-spectrum antibiotic “penbritin” [see previous Abstract] it was shown that when administered in single doses of up to 5 g. per kg. body weight orally or subcutaneously, or 2 g. per kg. intravenously, or in dosages of 500 and 100 mg. per kg. daily over a period of 12 weeks, penbritin was non-toxic to rats and mice, causing no arrest of growth and no biochemical, haematological, or histological abnormalities. In dogs, penbritin was better absorbed and gave more prolonged blood levels than phenoxymethylpenicillin or phenethicillin. It was shown to be evenly distributed throughout the body tissues apart from the kidneys and liver, in which concentrations higher than those in the serum were demonstrated. The antibiotic is excreted in the urine and bile and was found in considerable concentrations in these fluids. In mice its effectiveness against infections due to Staphylococcus aureus or Streptococcus pyogenes (Group A) was equal to that of the existing oral penicillins, while against infections due to Salmonella typhimurium or Klebsiella pneumoniae its activity appeared to be greater than that of tetracycline or chloramphenicol. This was in marked contrast to the titres obtained in vitro, in which only small differences were found.

A. Ackroyd


The authors have determined the serum concentrations and urinary excretions occurring in seventeen normal human subjects after various oral doses of "penbritin". The antibiotic was well tolerated and absorbed, peak serum concentrations varying from 2·19 \(\mu\)g per ml. after a dose of 250 mg. to 6·79 \(\mu\)g per ml. after one of 1,000 mg. being generally obtained about 2 hours after administration, compared with \(\frac{1}{2}\) to 1 hour after other acid stable penicillins, and significant serum concentrations were still present at 6 hours, while doubling the dose virtually doubled the peak serum concentration. Some 30 per cent. of a given dose was excreted in the urine over a 6-hour period. In four subjects who were given 500 mg. every 8 hours for 4 days, there was no accumulation of penbritin in the serum, the levels obtained on the 4th day being, on the whole, lower than those on the first.

For therapeutic trials the authors recommend that 250 mg. should be given 6-hourly for the treatment of infections due to Gram-positive organisms or to Haemophilus influenzae, a dosage of 250 to 500 mg. every 6 or 8 hours for urinary infections in view of the high concentration obtained in the urine, and 750 mg. or more 8-hourly for the majority of infections due to Gram-negative organisms.

A. Ackroyd


The authors report the results of microbiological and clinical studies with the new oral penicillin "penbritin". The results of the former studies, while in general similar to those reported by Rolinson and Stevens [above] showed a few comparatively minor differences. Whereas penbritin was active against many coliform organisms, the majority of strains of Escherichia coli were inhibited only by higher concentrations (5 to 50 \(\mu\)g. per ml.), at which even benzylpenicillin began to be effective. Organisms such as Aerobacter aerogenes, Proteus morgani, and Pseudomonas pyocyanae were uniformly resistant. In tests with Staphylococcus aureus, the minimum inhibitory concentration was shown to be dependent on the size of the inoculum, but this was not the case with sensitive coliforms. Generally, Gram-negative organisms which were resistant to a concentration of 10 \(\mu\)g. per ml. or more were resistant to other forms of penicillin at this concentration, although there were some exceptions. Cross-resistance of Staph. aureus was also not invariable. In a trial at Queen Mary's
Hospital for Children, Carshalton, Surrey, on eight selected children with well-established refractory urinary infections due to sensitive coliforms and/or streptococci of Group D, ten children with other infections, including one child with peritonitis due to Salmonella typhimurium, and another with meningitis due to streptococci in whom penbritin was injected intraventricularly in a dosage of 2 to 4 mg. daily for 4 days, rapid responses occurred to a 5-day course of 50 to 100 mg. per kg. body weight daily, but in six alimentary carriers of Salm. typhimurium and two of E. coli serotypes the infections were not cleared. Suppression of the faecal flora lasted until about 48 hours after the last dose.

Assay of serum or plasma showed that inhibitory levels (0.5 to 5 μg. per ml.) were attained and maintained for between 1½ and 7 hours after oral doses of 50 to 100 mg. per kg. per day. Assay of urine showed concentrations greatly in excess of those required for the inhibition of sensitive organisms (500 to 4,000 μg. per ml.). Excretion began within 3 hours, increased steeply during the next 3 or 4 hours, continued for 12 hours after the last dose, and ceased after 48 hours. Toxic effects were minimal and transient.

A. Ackroyd

PUBLIC HEALTH AND SOCIAL ASPECTS


MISCELLANEOUS


In experiments carried out at Ohio State University, Columbus, it was found that allantoic fluid from eggs which had earlier been inoculated with pus from infected lymph nodes from cases of cat-scratch disease agglutinated erythrocytes from rabbits and from hooded rats. Zoning phenomena suggested that an inhibitor was present in allantoic fluid and both the haemagglutinin and the inhibitor appeared to be sensitive to ionic concentration. The inhibitor was removed by diluting allantoic fluid with 0.28 M glucose and centrifuging. Normal rabbit and human sera also contained an inhibitor, which was eliminated by extracting with acetone and reconstituting the serum proteins in a phosphate buffer-hydrochloric acid mixture. Reconstituted sera from immunized rabbits and from two out of three human cases of cat-scratch fever specifically inhibited haemagglutination. Rabbits did not produce specific antibody after immunization with haemagglutinating fluids unless the fluids had been treated with glucose to remove the inhibitor.

Herpes simplex antiserum was found to inhibit the haemagglutination. However, the haemagglutinating virus did not kill chick embryos even after passage, “had no cytopathogenicity for cells in tissue culture” [no details given], and did not cause lesions on the rabbit cornea.

Janice Taverne


