IS GONOCOCCAL SENSITIVITY TO ANTIBIOTICS INCREASING IN NORWAY?*

BY

K. ØDEGAARD AND H. C. GJESSING

*From the National Institute of Public Health, Department of Bacteriology and the Bureau of Public Health,
Department of Venereal Diseases, Oslo, Norway*

Penicillin is widely known as the best and most suitable remedy in the treatment of gonorrhoea, but gonococcal sensitivity to penicillin decreased in Norway as well as in other countries (Gjessing, 1959; Gjessing and Ødegaard, 1964; Gästrin and Kallings, 1964; Reyn, Bentzon, Thayer, and Wilkinson, 1965).

Sensitivity to penicillin has been found to vary considerably in gonococci isolated from different geographical regions of the world. Reyn (1963) found that, whilst only 1 per cent. of gonococci from West Africa had reduced sensitivity to penicillin, the percentage from Manila in the Philippines was as high as 100. The explanation could be that because everyone in Manila had free access to antibiotics, the use of small doses for the treatment of gonorrhoea had resulted in decreased sensitivity. The percentage of gonococci with decreased sensitivity to penicillin can vary within the boundaries of individual countries (Interim report, M.R.C., 1961; Kallings and Gästrin, 1966).

The aim of this paper is to present the results of investigations showing the sensitivity of gonococci isolated at the National Institute of Public Health, Oslo, and to look for signs of change during the past years.

Material

Gonococci were isolated from 3,000 consecutive male patients at the Bureau of Public Health, Oslo, between May, 1959, and January, 1967. There were six groups of 500 patients taken in sequence. The sensitivity of the gonococci to penicillin, treatment, and eventual relapse, in the first 2,700 patients, has already been described (Gjessing and Ødegaard, 1964, 1965, 1966, 1967).

Methods

All gonococci isolated in this department since May, 1959, have been tested for resistance to penicillin G. The plate dilution method has been used with chocolate agar plates containing successively doubling dilutions of

penicillin G, giving a range of penicillin concentrations from 0.0075 to 1 unit/ml. and sometimes as high as 2 units/ml. Material was collected from several 18 to 20-hour-old colonies of gonococci and suspended in 0.5 ml. saline (during the past 2 years peptone-free broth has been used instead). One loopful was removed from this suspension and inoculated on to the plates. A staphylococcus strain, *Staph. aureus* P. 209, was used to control the penicillin content of the plates. A streptococcus strain which grows at 0.5 units/ml. but not at 1 unit/ml. was used to control the plates higher up the scale. Incubation was carried out at 37°C. in a humid atmosphere containing carbon dioxide. The results were read after 18 to 20 hours. The sensitivity of the gonococci to penicillin was registered as the minimum concentration at which no growth could be observed with the naked eye. We have considered strains with a minimum inhibitory concentration of ≥ 0.125 units/ml. as having a decreased sensitivity to penicillin.

A paper disk method was used for the other antibiotics (streptomycin, tetracycline, chloramphenicol, and erythromycin) and for sulfonamide. The antibiotic paper disks were prepared by the Bacteriological Department, Karolinska Sjukhuset, Stockholm. The sulfonamide disks contained 2.4 mg. each and the chloramphenicol disks 30 µg. Each of the other disks contained 50 µg. antibiotic. The technical method used is described by Ericsson, Högman, and Wickman (1954). The inhibition zones were measured in millimetres and the following designations were used: I sensitive, II fairly sensitive, III moderately resistant, IV resistant.

Results

Strains of gonococci with reduced sensitivity to penicillin were isolated from 137 (27.4 per cent.) of the 500 patients studied in Period I (May, 1959–June, 1961). This figure increased to 256 (51.2 per cent.) in Period IV (February, 1964–December, 1964) and then began to decrease gradually. In Period V (December, 1964–January, 1966) the number was 218 (43.6 per cent.), and in Period VI (January, 1966–January, 1967) it was 197 (39.4 per cent.).

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FIGURE.—Percentage of gonococci with reduced sensitivity to penicillin and to streptomycin, in 3,000 consecutive male patients examined between May, 1959, and January, 1967.

The manner in which the sensitivity of gonococci to streptomycin has fluctuated resembles that of penicillin, although to a much lesser degree: in Period I there were 20·8 per cent. strains with reduced sensitivity to streptomycin and this increased to 27·4 per cent. in Period IV, only to fall again to 23·6 per cent. in Period VI. The sensitivity curve for both antibiotics during the six periods can be seen in the Figure.

Sensitivity to penicillin has never been reduced so low that a strain could be called truly resistant, but reduced sensitivity to streptomycin has usually been so marked that the strain had to be termed resistant.

There was a decided connexion between sensitivity to penicillin and to streptomycin. The less sensitive the strain to penicillin, the greater the chance of its being resistant to streptomycin also. Where the minimum inhibitory concentration to penicillin was 1 unit/ml. or more, it followed that the strain was also completely resistant to streptomycin.

Reduced sensitivity has seldom been found amongst the other antibiotics, nor have we found any pronounced tendency towards an increase or a decrease of sensitivity to chloramphenicol, tetracycline, and erythromycin. We have in this series on two occasions only found decreased sensitivity to chloramphenicol, both in Period VI. During the six periods the percentage of strains with reduced sensitivity to tetracycline has varied from 0·2–2·8, and that of strains with reduced sensitivity to erythromycin from 0·4–4·0. The strains never showed total resistance to any of these three antibiotics.

The sensitivity tests to sulphonamides have in some instances an unfortunate tendency to show

resistance, when in fact the strain is sensitive. In spite of this, during the past 2 years, there have been only 3 to 4 per cent. of strains with decreased sensitivity to sulphonamides *in vitro*.

Discussion

Our investigation showed that the steady increase in the number of strains of gonococci less sensitive to penicillin reached a peak in 1964, when approximately 50 per cent. of the strains showed decreased sensitivity. The situation afterwards improved and the percentage fell to 39·4. The reason for this improvement could be the reinforcement of the treatment of gonorrhoea, especially in cases of relapse.

An increase in the frequency of penicillin-sensitive gonococci has also been found in Sweden during the past 2 years (Kallings and Gästrin, 1966). However, it is impossible at present to decide whether the decrease in the less sensitive strains is temporary or permanent; the problem is connected with the efficacy of treatment and the spread of less sensitive strains brought into the country from abroad.

Summary

In Oslo, Norway, an increase in the proportion of strains of gonococci less sensitive to penicillin culminated in 1964. During the past 2 years a change has occurred and a greater proportion of strains have been found fully sensitive to penicillin.

It has also been noted that more strains have become sensitive to streptomycin in the past 2 years.

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La sensibilisation des gonocoques aux antibiotiques, est-elle en augmentation en Norvège?

RÉSUMÉ

A Oslo, Norvège, une augmentation dans la proportion des souches de gonocoques moins sensibles à la pénicilline a atteint son plus haut point en 1964. Durant les deux dernières années un changement a eu lieu; on a trouvé qu'une plus grande proportion des souches est devenue complètement sensible à la pénicilline.

Il a été aussi observé que beaucoup d'autres souches sont devenues sensibles à la streptomycine durant les deux dernières années.