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Asymptomatic Significant Bacteriuria in the Non-pregnant Woman

II. Response to Treatment and Follow-up

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Summary: Short courses of nitrofurantoin and ampicillin produced an immediate cure in 80% of adult non-pregnant bacteriuric women. Of the subjects so treated, 55% remained cured at the end of one year. Over the same follow-up period 36% of untreated bacteriuric women developed a spontaneous remission of bacteriuria. Treatment failed to prevent the development of symptomatic infection, and the reinfections which followed successful treatment were more commonly associated with the development of symptoms than the persistent or relapsing infections in untreated or unsuccessfully treated subjects.

It is concluded that a search for bacteriuria in non-pregnant women is unlikely to be of value as a preventive measure, since in many instances it fails to detect urinary tract infection at an early stage and since treatment by methods suitable for large-scale use is ineffective.

Introduction

The prognosis of asymptomatic significant bacteriuria is unknown except in pregnancy, when it leads to acute pyelonephritis in up to 40% of cases (Kass, 1960). In this report we describe the response to treatment of the group of non-pregnant bacteriuric women described by Sussman *et al.* (1969). The clinical course of these women and that of a group of non-bacteriuric controls has been followed for one year.

The subjects included in the present treatment trial and the laboratory methods used were those described by Sussman *et al.* (1969).

Design of Treatment Trial

The initial treatment given to the bacteriuric subjects consisted of 50 mg. of nitrofurantoin or placebo four times daily for one week. Each bacteriuric subject was allotted a serial number on first attendance and the hospital pharmacist was provided with a randomized list of treatments to correspond with these serial numbers. At least four days after the completion of the initial treatment a "clean-catch" urine specimen was obtained during a follow-up home visit. Subjects who had failed to respond to nitrofurantoin as shown by bacterial culture were given a course of treatment with ampicillin 500 mg. four times daily for one week. All other subjects were given a course of treatment with placebo capsules. The nature of the treatments was unknown to the patients, bacteriologists, or clinicians, and the code was not broken until after the conclusion of the whole trial.

Follow-up of Bacteriuric and Control Subjects.—"Clean-catch" urine specimens were obtained from the bacteriuric subjects at a home visit at least four days after completion of the second course of treatment. Both the bacteriuric and the control subjects were seen either in the clinic or at home at six-monthly intervals. At each follow-up visit a standard questionary was completed to determine whether the subject had developed symptoms of urinary tract infection or had for any reason received treatment with antibacterial agents during the preceding six months. A further urine specimen was obtained at each follow-up visit, and all organisms grown from these specimens were stored and later identified. In the assessment of follow-up findings, *relapse* was defined as the reappearance of bacteriuria with an organism which was in every way identical with that originally isolated, apart possibly from its antibiotic sensitivity pattern. *Reinfection*, on the other hand, was defined as the reappearance of bacteriuria with an organism different from that originally isolated.

Effect of Treatment on Significant Bacteriuria

The results of treatment are shown in the Chart. Of the 107 bacteriuric women previously described, five refused to co-operate, two emigrated, and six were symptomatic before they could be included in the trial. The remaining 94 completed the first course of treatment either with nitrofurantoin or with placebo. Nitrofurantoin was given to 49 (52%) and the bacteriuria was cured in 39 (80%) and persisted in 10 (20%) of these. Resistance of the infecting organism to nitrofurantoin accounted for only one of the treatment failures. There were radiological abnormalities in four of the subjects who failed to respond to nitrofurantoin, but in the remaining five failure to respond could not be accounted for. No side-effects due to nitrofurantoin therapy were observed, but the dosage was low. Of the 94 bacteriuric subjects 45 (48%) completed treatment with the placebo. Bacteriuria persisted in 40 (89%) of these and cleared spontaneously in 5 (11%).

The second course of treatment consisted of ampicillin or placebo. Ampicillin was given only to those subjects who had failed to respond to nitrofurantoin. The remaining subjects—that is, those who had responded to nitrofurantoin and those who had received placebo—were all given a further placebo. Because of the high cure rate obtained with nitrofurantoin, only 10 subjects received ampicillin and only seven of these completed the course, which resulted in a cure in five of them. Since the number of subjects who received ampicillin was very small, the follow-up on the ampicillin treated group is not considered separately. In the 39 subjects cured by nitrofurantoin, the urine remained sterile in 32 (82%), while the bacteriuria recurred in 7. Of these recurrences, 4 (10%) were relapses and 3 (8%) were reinfections. In 4 (10%) of the 40 subjects

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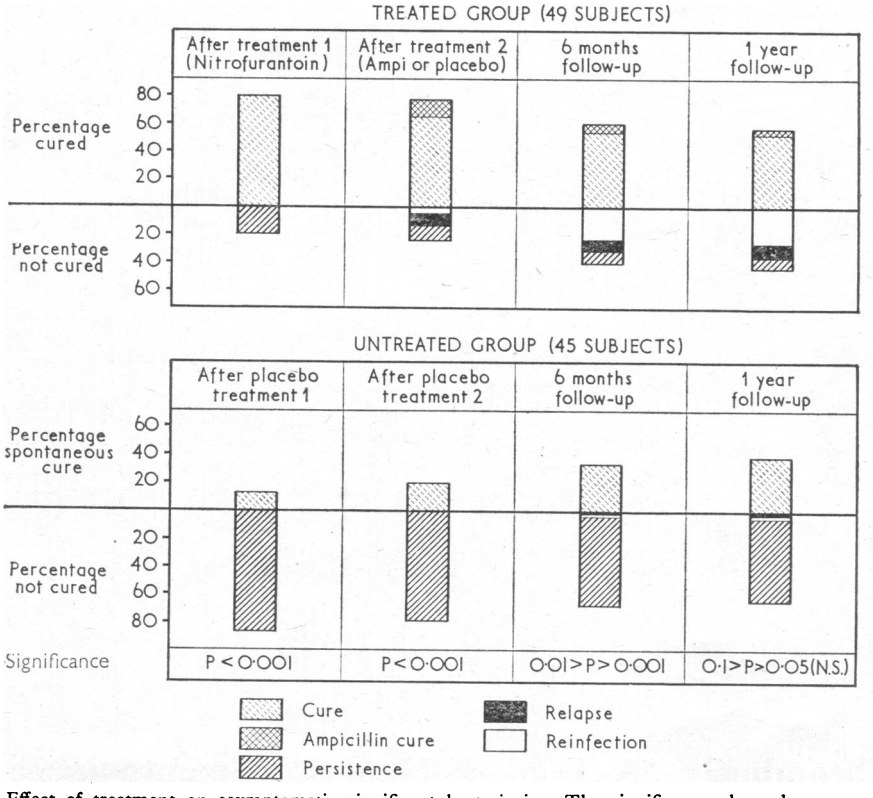
in whom bacteriuria had persisted after the first placebo had been taken the bacteriuria cleared spontaneously after the second placebo had been given. The urine of the five subjects cured by the first placebo treatment remained sterile after the second placebo. Thus at the end of both courses of treatment 37 of the 49 (76%) treated bacteriuric subjects were cured and in 9 of the 45 (20%) bacteriurics who had been given placebo spontaneous remission of the bacteriuria had occurred.

At six months follow-up (see Chart) reinfection had occurred in eight of the successfully treated bacteriuric subjects and at one year follow-up this number had increased to 10. In the placebo group spontaneous cure had occurred in an additional five subjects at six months follow-up and this number had increased to seven after one year. It is important to note that spontaneous remissions were confined to those bacteriurics in whom radiological abnormalities had not been found. At the completion of the one-year follow-up, therefore, 27 of the 49 treated bacteriurics (55%) still had a sterile urine. In the placebo group, 16 of the 45 subjects (36%) had undergone spontaneous remission. This difference was not significant (0·1>P>0·05). Thus after only one year there was no statistically significant difference between the treated and control groups.



Effect of treatment on asymptomatic significant bacteriuria. The significant values shown at the bottom were obtained by applying the χ^2 test to the number of subjects cured and not cured in the treated and untreated groups respectively.

The group of 88 non-bacteriuric control subjects was followed for a similar period of one year. Four of the 88 women (5%) developed significant bacteriuria.

Treatment and Development of Symptomatic Infection

During follow-up symptomatic infection was considered to have developed if a subject complained of frequency and dysuria lasting 24 hours or more, or if she developed loin pain and fever. On the basis of these criteria, 34 of the 94 (36%) bacteriuric subjects who had completed the treatment trial developed symptoms by the end of one year but symptoms of loin pain and fever had occurred in only two of them. Eighteen of those with symptoms were in the treated group and 16 were in the placebo group. This difference was not significant, and it may therefore be concluded that treatment did not prevent the development of symptoms.

Six of the 88 non-bacteriuric controls (7%) developed symptoms during the one-year follow-up period. In three of these the development of symptoms was associated with the presence of significant bacteriuria, whereas the urine was sterile in the remaining three subjects. None of the normal controls developed loin pain and fever. The difference between the rates of development of symptomatic infection in the bacteriuric and control subjects was highly significant (P<0·001). It therefore follows that asymptomatic significant bacteriuria leads to overt infection with symptoms which are not prevented by a short course of treatment sufficient to render the urine sterile.

In 4 of the 34 symptomatic bacteriuric subjects the urine was sterile at the time they attended the clinic, which was usually some time after the symptoms had subsided. In two of these subjects the general practitioner had prescribed antibiotic treatment for urinary tract infection before attendance at the clinic. In the remaining 30 subjects with symptoms the urine was infected. In 20 of these there was persistence or relapse of bacteriuria and in 10 the symptoms were associated with reinfection. Of the total of 15 subjects who had developed reinfection after treatment, 12 developed symptoms, whereas out of the total of 44 subjects with persisting or relapsing infections only 20 developed symptoms. This difference was significant (P=0·05) and suggests that symptoms were more likely to occur with reinfection than in subjects in whom infection persisted or relapsed after treatment. Symptoms were also more likely to occur in women with structural abnormalities on the excretion urogram. Thus symptoms developed in 14 out of 22 subjects (64%) included in the treatment trial in whom the pyelograms were abnormal and in 17 out of 49 subjects (35%) in whom intravenous pyelography had shown no abnormality. This difference was significant (0·05>P>0·02).

Discussion

The natural history of asymptomatic significant bacteriuria in the non-pregnant woman has not so far been adequately studied, nor has it been established whether a search for bacteriuria in this situation serves any preventive purpose.

So far the present study has contributed only towards an understanding of the short-term natural history of asymptomatic bacteriuria. After a follow-up of only one year 16 of the 45 untreated bacteriuric subjects (36%) had undergone a spontaneous remission. These spontaneous remissions were confined to subjects in whom no radiological abnormalities had been demonstrated. The finding of such a high spontaneous cure rate is supported by both experimental and epidemiological observations. Cox and Hinman (1965) showed that *Escherichia coli* is cleared from the urinary tract of normal human volunteers within 72 hours, and Kass *et al.* (1965) observed that bacteriuric adults in Jamaica have a remission rate of 25% per year. Freedman *et al.* (1965) found an even higher spontaneous cure rate among bacteriuric women in Japan.

Symptomatic infection developed in 16 of the 45 untreated bacteriuric women (36%). Loin pain and fever developed in only two of these subjects, whereas in the remainder the symptoms were frequency and dysuria. Comparison of these findings with the natural history of asymptomatic significant bacteriuria in pregnancy shows that the total incidence of symptomatic infection is similar. The distinguishing feature between the natural history of asymptomatic significant bacteriuria in pregnant and non-pregnant women is the severity of symptoms. Asscher *et al.* (1966) showed that in pregnancy the urine is continuously maintained at optimal *p*H for the growth of urinary pathogens. It may be that the greater severity of symptomatic infections arising in pregnant bacteriuric women is related to this.

A single course of treatment initially cured bacteriuria in 80% of cases, but was soon followed by relapses and reinfections, particularly in women who had been shown to have radiological abnormalities. One year after treatment, therefore, the cure rates among treated and untreated bacteriuric subjects no longer showed a significant difference. Not surprisingly, therefore, treatment failed to prevent the development of symptoms of overt infection. Moreover, it has been shown that the reinfections which followed treatment were more commonly associated with the development of symptoms than the persistent or relapsing infections in the untreated or unsuccessfully treated subjects. This would suggest that bacteriuric women may have developed tolerance to the particular organism harboured in their urinary tract and that treatment can temporarily upset this equilibrium. The occurrence of tolerance to the pyrogenic substances of Gram-negative bacteria in animals and humans with urinary tract infections has been demonstrated by McCabe (1963) and may explain the more frequent development of symptoms in subjects who are reinfected after treatment.

Our observations suggest that a search for significant bacteriuria in non-pregnant female populations does not satisfy either of the principal requirements of a good screening procedure. In many instances it fails to detect urinary tract infection at an early and reversible stage of its natural history (Sussman *et al.*, 1969), and treatment suitable for use on a large scale fails to alter its natural history. The present study still leaves an important gap in our understanding of the clinical significance of bacteriuria—namely, its relationship to the ultimate development of scarring and contraction of the kidneys and of renal failure. It is hoped that long-term follow-up of the bacteriuric and control subjects of this study will help us to provide an answer. At present it seems likely that even if persistent bacteriuria did lead to progressive renal damage its eradication would be difficult, costly, time-consuming, and probably hazardous.

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Treatment of Deep Vein Thrombosis. A Trial of Heparin, Streptokinase, and Arvin

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[WITH SPECIAL PLATE]

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Summary: Thirty patients with deep vein thrombosis of the legs of less than four days' duration were allocated at random to treatment with heparin, streptokinase, or Arvin under laboratory control. When the fate of the thrombi was assessed by objective techniques—phlebography and the ^{125}I-labelled fibrinogen test—the incidence of complete thrombolysis was greatest in the streptokinase group. Complications arose during treatment in each group but were least with Arvin. The natural history of the disease favours clinical but not always anatomical recovery.

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Introduction

The best treatment for deep vein thrombosis of the legs has yet to be decided. Comparisons between homogeneous groups of patients receiving different treatments have seldom been reported and, with few exceptions (Robertson *et al.*, 1968), rely on clinical signs for a measure of the effectiveness of treatment. This may be misleading, for clinical improvement is often complete despite persisting thrombus in the veins (Kakkar *et al.*, 1968).

The purpose of this paper is to report the results of treatment in 30 patients who were allocated at random to one of three treatment schedules. One group was given the anticoagulant heparin. Another received the plasminogen activator streptokinase (Kabikinase), which is known to have a thrombolytic effect (Browse *et al.*, 1968; Kakkar *et al.*, 1968, 1969a). The third group was treated with Arvin, a purified fraction of the