URINARY ANTISEPTICS*

A CRITICAL SURVEY

BY

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The intrusion of a urologist into the Section of Pharmacology, Therapeutics, and Anaesthesia may seem somewhat anomalous, but my excuse for accepting your invitation to open a discussion on the subject of urinary antiseptics is a desire to hear the views of others more qualified to speak on the action of drugs, and to put before you some personal experiences with the therapeutic agents in common use. If I have interpreted the term "critical" in somewhat too wide a sense, it is from a wish to point out some of the difficulties in the production of true antisepsis in the urinary tract. The subject of urinary antiseptics can be introduced, I think, by submitting two questions: What can we expect from such drugs as are employed to overcome urinary infections? and What is the basis of the pathology of such conditions?

Pathological Considerations

Drugs which have been shown to be inimical to the growth of certain bacteria are administered by mouth or into the blood stream, and ultimately reach the kidneys to be excreted into the system of urinary tubules and reservoirs before being evacuated from the body. In this evacuating system the antiseptic substance comes into contact with infected urine and, although by experiment *in vitro* sterilization at various degrees of dilution can be shown to take place, can we expect similar reactions to occur under the conditions in which the urine is formed and collected in the living body? The normal renal pelvis can be seen to empty itself in three to five minutes, and the passage of urine along the ureter occurs in a series of very rapid movements. It is a usual clinical experience to find that in patients where the contents of the renal pelvis and calices have become infected emptying is still more rapid, the capacity is less, and the walls of the cavity are in a hypertonic condition.

It would seem, therefore, that the sterilizing effect of any drug must be inefficient and of short duration as far as the renal pelvis is concerned. In the urinary bladder a certain degree of stasis is normally present, and here we can expect some action of antiseptic substances introduced into the urinary system. When mechanical obstruction is present, causing permanent retention of urine either in the renal pelvis or in the bladder, the growth of bacteria in the pool of urine probably exceeds the rate of excretion of any antiseptic substance in a concentration sufficient for it to exert an antibacterial action. The possibility of such solutions causing damage to, or irritation of, living tissue cannot be overlooked.

Speaking of the basal pathology of urinary infections as a guide to their treatment by drugs, I feel that I am on debatable ground, but the following is a brief outline of the conception which seems to me to fit most easily with clinical experience. The great majority of urinary infections are blood-borne. Exceptions are cases in which bacteria have been introduced directly into the bladder, almost always by a catheter, and cases in which free reflux can take place to the renal pelvis from a bladder already holding infected urine on account of the inadequacy of the uretero-vesical sphincter. Patients suffering from enlargement of the prostate with retention

of urine, and patients with large atonic dilatation of the whole uretero-pelvic system are examples of the latter condition.

It is difficult to prove that infection exists in the blood at any time, but a patient died recently from acute septic meningitis in which the same organism, *B. coli*, was present as had been found in the urine. The origin of such blood infection is equally difficult of proof. The gall-bladder must be considered in some cases, since patients have been cured of long-standing pyelitis by cholecystectomy. The bowel must usually be regarded as the source of the infection, and I would subscribe to the view that in any debilitated condition of the patient undue absorption of bacilli of the coliform group takes place through an unhealthy, but not necessarily diseased, mucous membrane. These bacteria are normally destroyed either in the cells of the mucous membrane or in the blood, but if the defensive mechanisms of the blood or body fluids are below normal some bacilli reach the kidney and infect the urine. In the ordinary uncomplicated cases of chronic renal infection two factors are therefore involved, both depending upon lowered resistance on the part of the patient: abnormal absorption of bacteria, and decreased destruction of them after entry into the body.

The acceptance of these theoretical considerations would explain why in so many cases the administration of what are described as urinary antiseptics must be ineffective. One of the main causes of such lowered resistance is mental exhaustion from overwork, worry, and strain. I would almost describe what is known as chronic pyelitis as a disease of professional men and women—doctors, lawyers, and clergymen—and ascribe the onset of the infection to one cause: long periods of intensive work without holiday. I have found that in only a small proportion of patients with bacilluria can one obtain a definite history of bowel disturbance. Such primary causes of increased bacillary absorption would be loss of the protective mucous covering from excessive purgation, damage of the epithelium from chronic intestinal stasis, or such inflammatory diseases as colitis, appendicitis, and cholecystitis. A bacilluria also frequently develops after operations on the bowel or on the female pelvic organs.

Management of Cases

A necessary preliminary to treatment is an exact diagnosis. Stone, tuberculosis, new growth, and obstruction are all frequent causes of continued pyuria and bacilluria, and are found in patients who have been treated without result by urinary antiseptics. The exact distribution of the infection should be determined by ureteral catheterization and bacteriological examination of the specimens. It will be found that pyelitis is often present on one or both sides without any local symptoms pointing to renal infection. Some estimate should also be made of the pathological anatomical changes which have been produced. In the early stages of the infection there is increased vascularity and swelling of the mucous membrane of the kidney, pelvis, and ureter, with rapid propulsion of their contents. In the late stages there is dilatation of the cavities, thickening of their walls, and a tendency to stasis.

It is usual for patients in whom a urinary infection has become established to suffer from a series of attacks between which the urine may be sterile and free from pus. These relapses may be due to true recurrence by reinfection of the urinary tract from the original source, or to recrudescence of an infection which persists on account of the changes which have been described. The swollen mucous membrane absorbs and holds the invading bacteria, which may penetrate and lodge in the sub-

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mucous coat until some general depressant cause excites them to fresh activity. Thickened areas of submucous infiltration can be observed in the bladder wall through the cystoscope. Each of these would seem to be a nidus of quiescent infection, and I imagine that similar patches occur throughout the wall of the ureter and the renal pelvis. Among the causes which produce such recrudescent infection are chill, constipation or diarrhoea, influenza, and mental anxiety. I am accustomed to tell these patients that their infection is like a smouldering fire, liable to be fanned to flame by any ill wind that blows, and only to be put out by a long period of general fitness and good health.

These questions have been elaborated to emphasize the difficulty of curing urinary infections by drugs. Until we can control the sources of infection, as well as ensure a free flow of urine from the kidney tubules as far as the exterior of the body, the search for a satisfactory urinary disinfectant is likely to remain unsuccessful.

Many remedies have been introduced and widely advertised as cures for urinary infections. Hexamine, with its allied forms urotropine, uraseptine, and cystopurine, remains, I think, the most useful of the urinary antiseptics. It is effective in closed cavities of which the contents are not too quickly evacuated and in which the growth of bacteria is not too virulent. I can recall two patients who have been kept in comfort by the regular administration of hexamine over a period of years: one man who had cystitis, and a certain amount of residual urine, which followed an injury to the spinal cord; and another man who has a pyonephrosis of moderate degree on one side, and whose general condition prevents its removal by operation.

Hexamine depends for its antiseptic action upon the liberation of formaldehyde which occurs when this drug meets with an acid medium. I have found that in most cases the acidity of the urine is sufficient to bring about this dissociation, and that only in exceptional cases is the administration of an acid necessary. The acid should never be mixed in the same prescription as the hexamine, and for the same reason hexamine should be given in the periods between meals, when the acidity of the gastric juice is at its lowest. Hexamine is of value as a prophylactic against infection of the urine, which may follow any operation or instrumentation upon the urinary tract, the female pelvic organs, or the bowel. In these cases the source of infection is temporary, and, if the excretion of bacteria takes place into an antiseptic urine, they are less likely to produce a permanent infection.

Hexyl-resorcinol, under the name of caprikol, has been tried as an alternative to hexamine. Its effect has been no greater, and there have been certain disadvantages in its administration. Some patients have complained of indigestion following its use; some have objected to swallowing the number of capsules required; and the restriction of fluid intake which has been suggested to obtain a sufficient concentration of the drug cannot be recommended. It is interesting from a pharmacological point of view to compare this latest member of the hexyl family with those well-established urinary disinfectants—buchu and uva ursi—which also depend for their antiseptic action upon phenol groupings.

It is generally recognized that an alkaline medium is inimical to the growth of the *B. coli communis*, and the beneficial results of thorough alkalization of the urine in the early stages of infection of this type are well known. Bacteriologists have found that some strains or members of the coliform group are equally intolerant of an acid medium, and this reaction is employed in the treatment of these infections by the production of a state of ketosis by means of a carefully regulated diet. In such condition ketones appear in the urine, and the acidity is

increased. Experiments *in vitro* have shown that the combination of acid and ketone has a powerful bactericidal effect.

Bacteria in culture tend to become accustomed to their surrounding medium. This would occur equally within the living body, and it is a matter of clinical experience that frequent changes in the reaction of the urine assist in its sterilization.

More recent additions to the list of urinary antiseptics are the dye preparations. Pyridium and neotropin are compounds of pyridine and, in addition to having a marked bactericidal action on cultures of cocci and *B. coli*, possess a distinct power of penetrating the tissues.

Neotropin is, I think, more easily tolerated by the patient. It is excreted in good concentration one to two hours after ingestion, and the urine remains coloured for several hours. The tissue penetration of dye preparations is an important factor, and this can be further utilized by applying them directly to the infected mucous membranes. I have used flavine and mercurochrome extensively in this way for bladder irrigation in a strength of 1 in 4,000, and for lavage of the renal pelvis and ureter in solutions of 0.5 to 2 per cent. according to the state of the mucous membrane. It is noteworthy that the mucous membrane of the pelvis of the kidney tolerates much stronger solutions of antiseptic substances used as topical applications than does the mucous membrane of the bladder. The use of both preparations by introduction directly into the blood stream has been advocated. The indications for intravenous treatment in urological cases are few. In patients with septicaemia due to the colon bacillus to whom injections have been given no lasting effect has been produced, while the immediate reactions were very severe.

The oldest of the dye antiseptics is methylene-blue. Its action is rather ill defined, but in combination with sandalwood oil in capsule form as santol-monol or V-noid capsules it is a useful sedative disinfectant in irritative conditions.

Conclusions

If I have confined my remarks to the treatment of that form of chronic urinary infection which is most frequently met with and commonly known as chronic pyelitis and cystitis, it is because in this disease most of the difficulties of producing a cure arise. In all other infections of the urinary tract a reliable treatment is well defined, but, when invasion by one of the coliform group of organisms is well established and recurrently maintained, the condition is notoriously resistant to treatment, and the search for a curative urinary antiseptic is likely to be prolonged. An attempt has been made to point out why this is so. The position may be summed up in one phrase: "Blame not the urinary antiseptic, but the mode of life of the patient." I would finally emphasize some points, attention to which may improve our results: the necessity of controlling the source of the infection; the building up of the natural bactericidal powers of the body; and the ensuring of a free flow of urine in an antiseptic fluid throughout all parts of the urinary tract.

Arrangements have been made for an international congress of criminal anthropology and psychology to be held in Rome next April, when the following subjects will be discussed: (1) aetiology, diagnosis, and prophylaxis of delinquent minors; (2) prophylaxis of criminality and penal laws; (3) the fundamental principles of biology and criminal biotypology; (4) prophylaxis of crime. Visits will be paid to the more important modern penitentiaries and institutions for the prevention of criminality and the re-education of delinquents.