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GENITO-URINARY INFECTION IN CHILDHOOD*

BY

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The subject of to-day's discussion, under slightly modified titles, has been reviewed at two previous meetings of this Section. In 1910 in London the discussion was opened by Dr. Box; the infection was assumed to be an ascending one because of the sex preponderance in females. Treatment by alkalis was recommended for acute cases, but for chronic cases there was little to be offered. The second occasion was at Winnipeg in 1930, Dr. Wilkinson opening the discussion. Two important advances were recorded: first, the work of Chown (1927) and Wilson and Schloss (1929), showing that the infection was usually blood-borne, was reviewed; secondly, the value of specialized urological investigation in chronic cases was emphasized.

Terminology

The term "pyelitis," implying acute infection of the renal pelvis, would seem to be a misnomer, for if the old view of an ascending infection is correct there must be a preceding cystitis, and "pyelocystitis" would then be a better term. It is my opinion that a relatively small number of cases, and these in girls, arise in this way. On the other hand, if the evidence of Chown and others is accepted, the infection in boys, and in the majority of girls, reaches the urinary tract through the kidney from the blood stream, and for these the term "pyelonephritis" is to be preferred.

Pyuria

Since the ultimate diagnosis of urinary infection rests upon the finding of pus in the urine, some comment may be made on this. It is often stated that a few pus cells may be found in the urine of healthy girls, and it is therefore important to have some guide as to what number of pus cells should be regarded as of pathological significance. A few years ago my house-physician, Dr. Cumings (1931), investigated this point and found that in eighty-eight healthy boys only three had pus cells in their urine, the greatest number being 4 cells per c.mm., while in eighty healthy girls fifty-five had pus cells, numbering up to 64 cells per c.mm. Dr. Alice Dickie also studied this aspect in her recent M.D. thesis, and I am grateful to her for allowing me to quote her figures. She investigated the urine of 900 children free from urinary infection and found that, using a high-power lens, the urine

from boys usually contained no pus, and never more than 1 cell per field; while, for the girls, more than 2 cells per field was abnormal. In both investigations the urine was passed naturally into a clean vessel after the glans or vulva had been swabbed, a drop being taken from a specimen that had been shaken up.

The fundamental importance of examining the urine microscopically for pus cells when any child is suspected of urinary infection cannot be too emphatically expressed. Merely to boil the urine for albumin is useless, because it is so likely to be present in other conditions, and, alternatively, if the amount of pus is slight albumin may not be detected. In the more severe instances of pyelonephritis a few red cells may be found in the urine, but their number is seldom sufficient to colour the specimen. It may be added that if the urine is to be cultured it is essential in girls to obtain the specimen by catheter, while in boys it may be collected aseptically after swabbing the glans with an antiseptic. Although culture of the urine is not essential for the diagnosis of urinary infection, which rests upon the finding of pus in the urine, a knowledge of the infecting organism will affect the choice of treatment, and therefore as soon as the presence of pyuria has been determined a specimen for culture should be obtained.

Aetiology

The two aspects to which I shall refer are the age and sex. With regard to the former, although pyelonephritis occurs throughout childhood it is most common in infancy; indeed, Craig (1935) was able to report sixty-one instances arising in the neonatal period. Graham's (1933) figures, based on 435 cases, demonstrate very clearly the distribution according to age (Table I).

TABLE I.—Age Incidence of Pyelonephritis in Childhood (435 Cases)

Age period ..	0-6 months	7-12 months	1-3 years	3-12 years
Number of cases	128	102	82	123

It will be seen that more than half the cases occur during the first year.

As to sex incidence, it is admitted that infection of the urinary tract is more common in girls, and this has been the accepted teaching for many years. Two results have followed: it has been used as a strong argument in favour of regarding the infection as an ascending one; and by stressing the incidence in females the possibility

* Read in opening a discussion in the Section of Diseases of Children at the Annual Meeting of the British Medical Association, Aberdeen, 1939.

that a urinary infection may underlie an unexplained pyrexia in a male child has been apt to be overlooked. Table II shows the sex incidence as reported by various observers.

TABLE II.—*Sex Incidence of Pyelonephritis in Childhood*

Author	Age Group	No. of Cases	Percentage of Females
Craig.. ..	Neonatal	61	34
Graham	Under 6 months ..	128	55
Gorter (1926) ..	Under 1 year ..	61	56
Author*	Under 2 years ..	50	60
Graham	Under 3 years ..	312	70
Gorter	Throughout childhood	114	73
Morse (1909) ..	" "	50	60
Graham	" "	435	75
Thomson (1910) ..	" "	25	84
Dickie	" "	43	81

* A series of cases analysed in the infants ward at St. Giles Hospital (L.C.C.).

The table shows what is now generally acknowledged—namely, that the preponderance of female cases applies to the period after infancy, but that during the first year or two boys are affected almost as often as girls, while in the newborn there is actually a majority of cases in boys. Now the high incidence of urinary infection in infancy has been ascribed to the ease of ascending infection through the contact of soiled napkins against the vulva, but this argument would only be valid if the sex preponderance in females was particularly noticeable in infancy. The figures given above show that at a time when ascending infection may be expected to occur most readily the sex incidence is practically equal. To my mind the figures afford a strong argument against the theory of an ascending infection.

The high incidence in infancy is probably connected with the fact that this is the age when* gastro-enteritis is most common, and there is frequently a history of some bowel upset immediately preceding the onset of pyelonephritis. It may well be that this disturbance is sufficient to lower the resistance of the bowel to the passage of bacteria, enabling them to gain the blood stream. In this connexion the occasional occurrence of rigors at the onset is probably of significance, for in childhood they usually connote a septicaemic state.

Symptoms

Neonatal Infection.—At this age the symptoms may differ a little from those in older children; for instance, the onset may be somewhat vague, and restlessness, vomiting, diarrhoea, diminished urinary output, or collapse may occur initially. Almost always the temperature is raised, and when this happens within three or four days of birth there is a tendency to call it "dehydration fever," assuming it to be due to the low fluid intake of the first few days. Dehydration fever settles quickly when extra fluid is given, but this does not exclude a urinary infection as a possible underlying cause, for the diuresis produced by the extra fluid might well be sufficient to alleviate a urinary infection. The diagnosis of dehydration fever should not be accepted until the urine has been shown to be free of pus. It may be added that at this age a high fever does not necessarily indicate a bad outlook; indeed, the most severe instances may have throughout a subnormal temperature.

Collapse.—This is also particularly likely to be encountered in young infants. In the attack the face appears grey and drawn, the lips are livid, and the forehead and scalp become pale. Such attacks may recur, and always indicate a severe infection, dangerous to life. They may come on gradually, and as gradually pass off, or may develop suddenly, the pulse and respiration becoming rapid, shallow, and irregular. At this age convulsions also are to be regarded as a bad sign.

Vomiting.—This is another important symptom of urinary infection in infancy. It may become persistent, and as it is often associated with loose, undigested, or offensive motions, it is easy to miss its significance and to rely for treatment on manipulations of the diet. When dietetic difficulties arise in an infant owing to repeated vomiting, the stools are unhealthy, and the weight remains stationary a urinary infection should always be suspected.

PYELONEPHRITIS AS A SECONDARY CONDITION

In infants the frequency with which pyelonephritis occurs as a secondary condition is not always appreciated. Of fifty patients under 2 years of age admitted to St. Giles Hospital in 1936–8 only sixteen could be classed as having uncomplicated or primary urinary infection. In the remainder the illness for which admission to hospital was sought was as follows:

Respiratory infection (bronchitis, pneumonia)	20 cases
Otitis media	2 "
Gastro-enteritis	6 "
Skin infections	5 "
Meningococcal meningitis	1 case

The proportion of cases secondary to gastro-enteritis is unusually small, but this is due to the fact that in an attempt to control ward infections the admission of infants with gastro-enteritis was stopped in 1938.

Dickie's similar investigation on forty-three children with *B. coli* pyelonephritis showed that the infection was primary in twenty and secondary in twenty-three. In her series gastro-enteritis accounted for one-third of the primary disorders. It is right to point out that in both these series the infants were drawn from definitely poor homes, and that, although urinary infection may occur in any social grade, its occurrence as a secondary disease is more likely to be encountered in children from poor and overcrowded homes, where the standard of resistance to infection is low.

The part that vitamin deficiency plays in promoting urinary infection is difficult to assess, but that it is probably of importance is indicated by the rarity of pyelonephritis in breast-fed infants. In my series there were twenty-one infants under 9 months old, and none of these was breast-fed. It is well known that both rickets and scurvy may be complicated by urinary infection, especially scurvy, and in the few fatal cases of infantile scurvy that I have met with pus cells have usually been present in the urine before death.

Treatment of Acute Infections

The treatment of pyelonephritis may be divided into the management of acute, and chronic or recurrent, cases. For many years the treatment of choice for acute pyelonephritis has been to give alkalis in doses sufficient to render the urine alkaline, and the question that now arises is whether this treatment should give place to mandelic acid or sulphanilamide therapy. The first point is whether alkalis alone can bring about a cure; I submit that the long experience with alkaline treatment leaves little doubt

that complete cure is usually obtained. This aspect was particularly investigated by Neale (1931), who analysed 130 cases, and found that when cure came about it was complete, and that in later years there was no evidence of permanent or progressive damage to the kidneys. The second point is whether the alkaline treatment is of itself at all harmful to the patient, and here again alkalis show up well. They can be given in large doses to children of any age, and their only limitation is that in infancy they may sometimes cause a slight diarrhoea. Even this is lessened if bicarbonates and citrates are used in a mixture instead of relying on citrates alone. We have, then, in alkalis a harmless efficient remedy for the majority of children with acute pyelonephritis. Mandelic acid has the disadvantage that it is an acid preparation, which often has to be combined with extra acidifying agents, and for a child who is acutely ill with a high temperature treatment by alkalis is, on general principles, to be preferred to treatment with acids. Sulphanilamide overcomes this difficulty in that it may be combined advantageously with alkalis; but its toxic symptoms, although admittedly uncommon, are greater than those of alkalis alone. Perhaps the most important point of all is to know whether there is in the background some congenital abnormality of the urinary tract. Now, although treatment with alkalis alone will clear up the majority of cases of acute pyelonephritis, it may relieve, but certainly will not cure, a case with urinary tract deformity. If it is found that a thorough trial of alkaline treatment over a period of three weeks or so is not leading to a cure, special urological investigations, mentioned later, should be undertaken to determine the presence and nature of any congenital deformity. On the other hand, treatment of acute cases with mandelic acid or sulphanilamide is likely to sterilize the urine even in the presence of a congenital deformity, and this may lull the physician into a false sense of security by masking the essentially chronic nature of the condition, and so deterring him from instituting a full urological investigation. The position may be summed up by saying that if acute cases are to be treated with mandelic acid or sulphanilamide, then after the urine has been sterilized the patient should be submitted to a full urological investigation in case some congenital deformity is being overlooked; but, by treating these cases in the first place with alkalis, special investigations need only be carried out in the small group that proves resistant to treatment. These may then be treated with either mandelic acid or sulphanilamide. The relative merits of these two preparations are considered later.

Alkaline Therapy

The most useful alkalinifying agent is potassium citrate, which must be given in an amount sufficient to render the urine strongly alkaline. In practice it is easy enough to bring the urine down to neutral, but it is often difficult to get it beyond this point. Another practical point is that it is useless to give alkalis by day and allow the urine to revert to acid during the night, and therefore treatment must go on through the twenty-four hours. No exact directions for dosage can be given, because this must be determined by testing each specimen of urine with litmus as soon as it is passed; such doses as 10 grains every three hours day and night for an infant, and four times this dose for a child of 6 or 7, are often required. The alkaline reaction of the urine should be maintained for at least ten days after the symptoms have subsided and the urine has become free of pus. It sometimes happens that although the temperature falls the urine becomes more and more offensive, and it is then useless

to continue with alkalis; a change to mandelic acid or sulphanilamide would be indicated.

The mode of action of alkalis is not fully understood. Hare, Lepper, and Martland (1928) have shown that the urine cannot be made alkaline enough to become bactericidal, and it would seem that the beneficial effect is to a large extent the result of diuresis. In this connexion it is of interest that "dehydration fever" of the newborn, which is sometimes associated with pyuria, quickly responds as soon as sufficient fluid is given to promote diuresis.

Treatment of Chronic Infections

The development of urological technique suitable to young children has demonstrated the fact that when an acute infection, in spite of treatment, becomes either chronic or recurrent, this is generally associated with some stasis of urine: occasionally this may be caused by a stone, but is much more likely to be due to some congenital abnormality in the architecture of the urinary tract. The old diagnosis of "chronic pyelitis" has rightly been given up, for, faced with a child with a chronic urinary infection, the physician should co-operate with the urologist in an attempt to discover if there is an underlying cause.

The following methods of investigation are at our disposal. First, the type of infecting organism must be ascertained, for this may influence the choice of drug treatment. Secondly, an intravenous pyelogram should be carried out in order to ascertain not only the anatomical outline of the renal pelves and ureters but also to gauge whether the secretion of the kidneys is in any way delayed. Uroselectan B or perabrodil is generally employed, the amount injected being not less than 5 c.cm., otherwise a clear picture is not likely to be obtained. At 2 years of age the dose should be 8 c.cm., at 5 years 10 c.cm., increasing to 15 c.cm. at 12 years. By this means a pyelogram can be obtained even in young infants, the youngest in my experience being a baby of 9 weeks. Such abnormalities as horseshoe kidney, hydronephrosis, double ureter, kinks or stenoses of the ureter may be revealed. The next step is a cystoscopy, and ascending pyelography. In a female infant it is possible to perform a cystoscopy and pyelography from birth; in the male, a cystoscopy is sometimes practicable from birth, but ureteric catheterization cannot be undertaken before the age of 2 or 3 years. Lastly comes the investigation of renal function by such methods as the blood urea, urea-concentration test, and urea-clearance test. Unfortunately it not infrequently happens that abnormalities are bilateral, and both kidneys are damaged, so that surgical relief may be impracticable; on the other hand, if the deformity is unilateral, surgical intervention may be hopefully undertaken with the prospect of the child returning to normal health.

The next point concerns the sterilization of the urine. Treatment by alkalis is generally quite useless, and although extensive trials have been made of such treatments as hexamine and similar urinary antiseptics, vaccines, and sera, these methods are mostly without effect. Recently, however, there have been two important advances in treatment. In the first place we have the salts of mandelic acid; and, secondly, the sulphanilamide group of drugs. Both have the great advantage for children that they are effective when given orally.

Mandelic Acid

The two preparations now generally used are ammonium mandelate and calcium mandelate. Both salts have the

advantage of making the urine strongly acid, although even so it is generally necessary, in my experience, to give some additional acidifying agent. Calcium mandelate is insoluble in water, but has the advantage of being tasteless. Ammonium mandelate in the form of the elixir is not unpalatable, and a mixture similar to the elixir in use at Great Ormond Street is as follows:

Ammonium mandelate, 26 grains*
Liquid extract of liquorice, 5 minims
Elixir of gluside, 1/5 minim
Water to 1 drachm

* Equivalent to 1½ grammes of mandelic acid.

The dose required varies according to the age: at 1 year at least 3 grammes of mandelic acid should be given in twenty-four hours, equivalent to two teaspoonfuls of the above mixture, while double this amount will be needed for a child of 10 years.

It is essential to keep the urine sufficiently acid, and it is necessary to test a specimen each day. For this purpose a few drops of methyl-red should be added to a third of a test tube of urine; if the urine is acid enough it develops a pink colour, otherwise it becomes orange-coloured. Should the mandelate by itself not produce the necessary acidity, an agent such as ammonium phosphate must be given. A suitable mixture is:

Ammonium phosphate, 7½ grains
Liquid extract of liquorice, 5 minims
Syrup of lemon, 15 minims
Water to 1 drachm

The amount required will be indicated by the methyl-red reaction; from two to six teaspoonfuls a day may be necessary. The administration of mandelic acid should be maintained for a week after the urine has become sterile, otherwise a relapse may easily occur.

Although mandelic acid therapy has proved to be a most valuable weapon it has its limitations. The undesirability of giving strongly acid preparations in acute cases has already been mentioned. In chronic cases there is often considerable impairment of renal function, and it may then be almost impossible to get a sufficient concentration of the drug in the urine to render it sterile. The type of infecting organism is also important; for while infection by *B. coli* or *Streptococcus faecalis*, or a mixture of these, responds favourably, those organisms that are associated with an alkaline urine, such as staphylococci, and organisms which split urea down to ammonia, such as *B. proteus*, are not destroyed by this treatment.

With regard to results, Braasch (1937) reported mandelic acid to be bactericidal in 80 per cent. of cases of uncomplicated urinary infection. Summerfeldt and Brown (1938), reporting on fifty-two children, twenty-one of whom had chronic infection, found that 12 per cent. did not respond, while 20 per cent. suffered a recurrence of symptoms within twelve months. Droller (1938) compared thirty-one cases treated with mandelic acid with twenty cases treated with sulphanilamide; in the first group 71 per cent. were cured and in the second group 75 per cent. Such figures give a fair picture of what may be expected with this line of treatment.

SULPHANILAMIDE

The sulphanilamide group of drugs—prontosil, pro-septasine, ueron, sulphapyridine—since their first introduction to clinical medicine a little more than two years ago, have already established a world-wide reputation,

and have been shown to possess such a wide sphere of usefulness that it is not surprising to record their definite value in urinary infections. One effect of this has been to limit quite sharply the use of mandelic acid. This is shown in the following chart, which records the amount of

Chart showing amount of mandelic acid dispensed during each quarter of the year at the Hospital for Sick Children, Great Ormond Street.

mandelic acid in pounds dispensed at Great Ormond Street in each quarter of the year since 1935.

Sulphanilamide is most effective in a slightly alkaline urine, and it is advantageous to prescribe twenty or thirty grains of alkali a day. This dose is of course not comparable to the larger doses given in the alkaline treatment of acute urinary infections. The concentration of sulphanilamide required for sterilization of the urine—50 mg. per 100 c.cm. of urine—can usually be obtained without difficulty even in the face of impaired renal function, which gives the drug a definite advantage over mandelic acid. Once again the bacteriology of the urine is important, for the sulphanilamides usually give a prompt success in *B. coli* infections, and will often clear up that most resistant organism *B. proteus*, but their action against the *Streptococcus faecalis* is disappointing: mandelic acid is here the weapon of choice.

The dose of sulphanilamide varies with the age, but it is more effective to give a relatively big dose over a short period than prolonged administration of a small dose. To an infant of 6 months 0.25 gramme (half a tablet) six-hourly, and four-hourly at 1 year, is generally tolerated without difficulty, while in the second half of childhood 0.5 gramme may be given every four hours. The usual precautions against giving sulphur-containing drugs or foods such as aperient salts and eggs must be observed in order to lessen the chance of cyanosis. Toxic effects from these drugs are, however, uncommon; the one that in my experience has caused most difficulty has been vomiting, although that has not been at all common; should it occur, it will continue until the drug has been completely withheld. A morbilliform type of eruption occasionally arises, and I have seen it in one case. The rash disappears when the drug is withdrawn. The most serious complication is agranulocytosis; but fortunately it is rare, and I am glad to say that I have not met with an instance. Bigler and others (1938) have shown that there is often a slight drop in the leucocyte count, but this is not sufficient to influence the response of the patient.

I have purposely not drawn any distinction between the various preparations that may be used, for with regard to urinary infection their differences are scarcely apparent. The dose is the same whichever preparation is used. As

with mandelic acid, sulphanilamides should be continued for a week after the urine has become sterile, otherwise relapses may occur.

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ANAESTHESIA IN DENTAL SURGERY*

BY

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The majority of dental operations in this country are performed in the dental surgery under nitrous oxide anaesthesia on ambulant unpremedicated patients. In most cases this agent affords a pleasant and rapid induction, quick recovery, and freedom from after-effects. Ninety per cent. are managed satisfactorily, but the remainder present difficulties, mainly on account of the weak anaesthetic properties of nitrous oxide. Discussion of the conduct of anaesthesia for major dental operations and the special problems of anaesthesia for dental work in children will not be undertaken in this brief review, which deals with the problems arising in the 10 per cent. of patients who prove difficult under nitrous oxide anaesthesia in the dental surgery. Later, cyanosis, anaemia, and respiratory obstruction are discussed, since it is felt that a fuller appreciation of the underlying physiology and pathology of these conditions will make for smoother and safer anaesthesia.

The patient may present difficulties on account of his psychological approach to anaesthesia or because of resistant physical qualities which are difficult to overcome with a weak anaesthetic such as nitrous oxide.

Psychological Considerations

The problem here is to prevent disturbances during induction. The energy for resistance is dissipated early during anaesthesia, so that maintenance is no more difficult than in the average patient. The prospect of being rendered unconscious is not a pleasant one; addiction to anaesthesia is unknown! In the great majority of adult patients this natural apprehension is not sufficient to disturb the even course of anaesthesia. Two classes need special attention—one the undisciplined with poor self-control; the other the basically nervous but superficially controlled patient, who typifies the "stiff upper lip" school and who may not betray any mental disturbance until well after induction is begun. This first type is

uncooperative from the beginning, but the patient whose training has enabled him to mask his fear by rigid self-control presents a different problem. The early part of induction is smooth, but as soon as conscious control is lost his basic fear is manifested by struggling.

For both these types premedication is valuable. It varies from reassurance, the patient's own particular fear being dealt with, to the use of sedative drugs. These should not depress the patient to such an extent that he is unable to leave the surgery within a reasonable time. Simple but effective premedication is 10 grains of aspirin the night previously, and this dose repeated two hours before the operation. If the patient dislikes induction by inhalation it can be avoided by giving a small intravenous dose of barbiturate—for example, 0.2 gramme of evipan or pentothal—and continuing anaesthesia by nasal administration of nitrous oxide. Small doses of pentothal are rapidly eliminated, so that recovery is scarcely if at all longer than after nitrous oxide alone.

Physical Considerations

Certain types of patients are notoriously difficult to anaesthetize, and their resistant qualities are most evident when a weak anaesthetic such as nitrous oxide is used. Although the anaesthetic-resistant patient is usually robust and often hard-living, occasionally a small wiry man displays a resistance which his appearance belies. Resistance to anaesthetics is markedly increased by alcoholism or any other drug addiction.

Nitrous oxide is the weakest of all anaesthetics. If it is to be used successfully for the anaesthetic-resistant patient its weak action has to be reinforced by reducing the oxygen intake to levels where asphyxial signs appear. There is only a narrow margin of anaesthesia between response to a surgical stimulus and asphyxial spasm. An attempt to subdue a difficult patient with nitrous oxide alone results in anoxial muscular spasm which may make operating difficult. If the anaesthetist is unwise enough to persist, spasm of the adductor muscles of the larynx may follow, with resultant respiratory obstruction. Artificial respiration or inflation of the lungs is then impossible because of the tightly closed glottis. The situation is alarming. Since muscular rigidity passes off before death, artificial respiration must be continued so that the lungs will be immediately expanded on relaxation of the spasm. This state of affairs can be avoided by combining the nitrous oxide with a more potent anaesthetic which will allow the introduction of enough oxygen to avoid production of anoxial spasm. The most useful drugs for this purpose are the barbiturates, given intravenously, or ethyl chloride. Anaesthesia should be induced by the former in cases where it is considered improbable that nitrous oxide will be adequate. The extra time involved in the preparation of a sterile intravenous injection is amply justified by the results. If the operation has been started with nitrous oxide and the patient unexpectedly proves to be unmanageable it is technically impossible to give an intravenous injection, and the supplemental use of ethyl chloride is of value because of its potency, ease of administration, and rapidity of action.

If it is decided to reinforce nitrous oxide by the use of a barbiturate, a small dose (for example, 0.2 to 0.4 gramme) of evipan or pentothal injected rapidly will produce unconsciousness. A large proportion of the drug is carried to the brain by the vast carotid circulation, causing immediate unconsciousness. Anaesthesia is continued at once by nitrous oxide administered nasally. Provided a clear airway is maintained the barbiturate can

* Read in opening a discussion in the Section of Pharmacology at the Annual Meeting of the British Medical Association, Aberdeen, 1939.