TREATMENT OF *B. COLI* PYELITIS WITH ALKALIS

BY

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The variety of therapeutic methods and substances advocated for the treatment of *B. coli* pyelitis suggests that we lack any single established and successful form of therapy. I believe that failure with alkaline therapy generally results from either faulty technique or a mistaken diagnosis.

To give even fairly large doses of sodium bicarbonate, with or without potassium citrate, until the urine turns red litmus paper blue will no doubt suffice in some cases. But in a large number it will cause only temporary improvement or none at all. It is usual, therefore, to try in succession alternating periods of acid and alkaline salts, acid salts and hexamine, hexyl-resorcin, mercurochrome, acriflavine, ketogenic diets, colonic lavage, washing out the renal pelvis, vaccines, sour milk, lactose, *B. acidophilus*, and so on, when generally all that is required is a careful adjustment of the dose of alkali, or of the manner in which it is given, and an increase in the fluid intake. In my experience none of these other methods, with the exception of the ketogenic diet, which is referred to later, gives consistently satisfactory results in any large series of cases and over long periods, though in individual instances brilliant success may be achieved at times with all of them. It is not only that the therapeutic results are uncertain, but valuable time may be lost in trying one form of treatment after another, whilst an acute case is passing into the often incurable subacute and chronic stages. Again, many patients may waste large sums of money on expensive drugs, sea voyages, prolonged sojourns at watering-places and spas, and similar therapeutic measures.

Effective Alkali Therapy

We possess in alkali therapy a simple, cheap, and effective remedy for all uncomplicated cases. I can recall no instance of failure except where subsequent investigation has revealed the presence of a urinary calculus, an obstruction to the flow of urine, or a mistaken diagnosis. The method is indeed of diagnostic value, for failure to relieve in a very short time may be regarded as an almost certain indication of some mechanical complicating factor.

The successful treatment of *B. coli* pyelitis with alkalis depends chiefly upon careful attention to detail: essential factors in the method are the production of a copious diuresis and a sufficiently alkaline urine. Clinical trials show that neither alone is effective, though of the two the mechanical flushing out of the urinary passages is probably the more important. A certain degree of alkalinity of the urine tends to inhibit the growth of *B. coli communis*, though it may flourish sometimes in exceedingly alkaline urines, especially *in vitro*. Recent observations suggest that inhibition of growth of the bacilli is more satisfactorily accomplished when the urine has been rendered unusually acid, as with a ketogenic diet. But the precise significance of the reaction of the urine in relation to the growth, or inhibition of growth, is not yet known.

Importance of Rest

All acute and pyrexial cases must be confined strictly to bed until the temperature has become normal, all signs and symptoms have disappeared, and the urine is normal in appearance, at least to the naked eye. The temperature must be carefully taken and closely watched.

At first four-hourly readings will be required, but later a record of the morning and evening temperatures will be sufficient. Rectal temperatures are not essential, but if temperatures are taken orally it is important that the thermometer be left *in situ* for at least eight minutes. This applies to all thermometers, whether purporting to be "timed," "tested," "guaranteed," or not. Incidentally, it should be noted that the normal daily range of temperature for an adult confined to bed should be from about 97° to 98° F. A regular evening temperature of 98.4° under such conditions is abnormal. An accurate record of the temperature is essential during the period when the patient is first allowed up on a couch or chair. A slight increase of temperature at this stage requires either a readjustment of the dose of alkalis or sometimes a return to bed. For all practical purposes the temperature chart as a guide to the amount of physical exertion permissible has the same significance as in cases of pulmonary tuberculosis. As in many other acute infective diseases after the temperature has returned to normal a weekly estimate of the sedimentation rate of the red blood corpuscles is a useful index of the general progress of the case.

Fluid Intake and Output

In adults at least six pints of fluid, and preferably more, should be consumed every twenty-four hours during the acute stages. The total quantity of fluid is more important than its actual nature, though the best fluids to give are water, barley water, lemonade, and orangeade, to any of which glucose may be added when severe anorexia prevents the taking of solid food. Weak tea, and skimmed milk with or without soda, may also be given. It is important to have a record of the total quantity of urine passed each twenty-four hours. A significant decrease in the output of urine almost always means that the intake has been allowed to fall below the required minimum and is evidence of careless nursing.

Diet and Milk

In all stages this can safely be left to the wishes of the patient. The acutely ill case with marked pyrexia, rigors, or vomiting will not desire much, and may be kept on fluids with additional glucose, or milk, which may be diluted if necessary. Some authorities are opposed to the giving of milk, but I have seen no ill effects from its use, and provided the patient can tolerate it I generally allow it in the early stages, before solid food can be taken. Skimmed milk is often more agreeable than whole milk, and is especially useful for children. Where large quantities of milk are being taken the amount should of course be reckoned in the total fluid consumption for the twenty-four hours. There is no special reason for limiting the protein intake in any stage of the disease as renal function is not impaired.

Associated Constipation

There is no doubt that *B. coli* infections of the urinary tract are often associated with constipation, especially in women. Nevertheless, diarrhoea is even more harmful, and fluid motions should be avoided. It is better, therefore, not to give purges in any stage. Constipation can always be overcome by regular doses of liquid paraffin or petrolagar, and, if necessary, by an occasional simple enema. It should be remembered that large doses of alkalis themselves have a slight laxative action. In chronic cases liquid paraffin may be supplemented by abdominal massage and exercises.

Administration of Alkalis

Clinical experience shows that the optimum degree of alkalinity is a minimum pH of 7.6—that is, a little more alkaline than the normal reaction of the blood. As the

early morning samples of urine are usually the most acid of the twenty-four hours, it is sufficient in most cases to ensure that this specimen be of the required reaction. Should the early morning specimen become less alkaline than pH 7.6 then the dose of alkali must be increased without delay, as otherwise later samples will show, often in the course of a few hours, increasing acidity and a return, or increase, of pus, albumin, and bacilli in the urine, followed shortly by a rise in temperature. Litmus paper should never be used for testing the reaction of the urine. This can be estimated accurately, quickly, and easily in the following manner. Two or three drops of a 0.1 per cent. solution of brom-thymol-blue (two ounces of this solution may be conveniently kept for the purpose in a stoppered drop-bottle) are added to about 3 c.cm. of urine in an ordinary test tube, and the resulting colour compared with a series of standard colour tubes or disks.* It is only necessary to remember that (a) the specimen tested should be one passed before breakfast; (b) it should be quite fresh and preferably still warm from the natural heat of the body; (c) that only the gentlest motion should be used in mixing the dye and urine (violent agitation or even inversion of the tube will cause CO₂ to be taken up from the atmosphere and give too "acid" a reading); and (d) the test tube should be clean, and either first washed with distilled water or with tap water and then rinsed with a preliminary sample of the specimen to be tested. As the latter is always dilute, owing to the diuresis, the natural pigment of the urine does not interfere appreciably with the colour comparison, though if necessary this can be compensated for by holding a tube of the urine, without added dye, behind the standard colour tubes. At a pH of 7.6 the resulting colour should be a distinct dark blue, but at reactions less alkaline than this a greenish tint will become increasingly more evident. It is helpful to explain to patients who are sufficiently recovered to carry out this test for themselves that a pH of 7 on any of the standard scales corresponds to neutrality, consecutive numbers below this to increasing acidity, and above it to increasing alkalinity.

Technique of Dosage

In acute cases with severe symptoms it is necessary to increase the dosage rapidly. It has been found best to give by mouth a mixture of equal parts of sodium bicarbonate and potassium citrate, as large doses of the former alone tend to induce vomiting, whilst the latter in appreciable amounts may cause diarrhoea. By giving both salts in equal quantities these difficulties are avoided. I usually commence with the following mixture:

R.	Sod. bic.	}	...	...	...	...	āā gr. xxx
	Pot. cit.	}	...	...	...	...	
	Syr. aurantii	...	...	...	...	...	ṡ xxx
	Aq.	...	...	...	...	...	ad 3 jss

given either one-, two-, three-, or four-hourly, according to the urgency of the symptoms, and continued until the volume of urine passed is obviously increasing, and the reaction is sufficiently alkaline to brom-thymol-blue—that is, the pH is 7.6. At this point the dose may be reduced to three-, four-, or six-hourly, so long as the reaction of the urine does not fall below the required level. The dose which then maintains the early morning specimen of urine at this reaction is the optimum dose, and must be continued as explained later. With rare exceptions, in those cases where there is no mechanical obstruction to the flow of urine, a satisfactory diuresis of 60–70, or more, ounces, of urine per twenty-four hours and a sufficiently alkaline reaction is attained in about forty-eight hours. The urine is by then practically clear to the naked eye; if

not, then a little acid or household vinegar should be added to eliminate cloudiness due to the precipitation of phosphates, and the pyrexia and pain will have disappeared. Thereafter, by trial, the dose may be reduced to that which will just maintain a minimum pH of 7.6 in the early morning specimens of urine. The mixture should be given strictly to time and in acute cases through the night as well, even at the expense of disturbing sleep. In subacute and chronic cases at least one dose should be taken about 3 a.m., for which purpose an alarm clock may be provided. A slight increase of dosage is often called for when the diet is augmented, and especially when the patient first gets up and begins to walk. On these occasions it will usually be found that the urine has become slightly less alkaline and, if this be not corrected, a rise in temperature and a recurrence of symptoms will follow shortly. In early cases with intractable vomiting sodium bicarbonate may be given per rectum as a 3 per cent. solution until oral administration becomes feasible, though this is rarely necessary. Extra fluids may also be given per rectum in such cases. The total dosage of alkalis per twenty-four hours varies with every case and in the different stages of the disorder. In my own series the maximum dose in the acute stage has ranged from 240 to 1,100 grains per twenty-four hours. It is, however, rarely necessary to maintain the maximum dose for very long.

Difficulties of Administration

It cannot be denied that large doses of these alkaline salts, however flavoured, are unpleasant to take. Nevertheless I have never found it necessary to abandon treatment for this reason. Serious difficulty from this cause is only encountered in neurotic individuals who from long habits of indulgence are lacking in self-discipline, and such are notoriously susceptible to persuasion. In a protracted case it is sometimes wise to change the flavouring agent, and aqua menth. pip., with or without chloroform water, may be preferred. It is also a useful plan to add a teaspoonful of sugar to the mixture before taking it. Judicious spacing of the doses is a most important matter. To crowd the doses too closely or to give too strong a dose is to court disaster. The ideal is to spread the doses as evenly as possible through the twenty-four hours, though the greater number must inevitably be taken during the daytime. The total quantity of alkali in each dose should, however, be as small as possible. Thus it is better to prescribe drachm doses of alkali (30 grains of potassium citrate and of sodium bicarbonate) at two-hourly intervals through the day, beginning at 8 a.m., with one dose at 3 a.m. (total for twenty-four hours, 540 grains), than four doses of 135 grains (total alkali) and one similar dose at 3 a.m. A useful rule, therefore, is to increase the *number* of doses per twenty-four hours before increasing the *strength* of each dose. Since it is an advantage to encourage as large an intake of fluid per diem as possible there is no objection to diluting each dose, and this greatly diminishes the unpleasantness of the mixture. It is also advisable to ensure that the medicine is not swallowed at one gulp. At least ten minutes should be taken over each dose. Attention to such details as these may well make all the difference between success and failure.

Causes of Failure

By far the most frequent cause of failure is an insufficient dose of alkalis. In a straightforward case the major symptoms—pain, tenderness, rigidity, rigors, and vomiting—will have subsided within about forty-eight hours of the urine attaining an alkalinity of pH 7.6. The temperature, too, will have fallen approximately to normal. The urine, though still containing pus and

* At the cost of a few shillings suitable colour standards for the brom-thymol-blue range can be obtained in the form of tubes from the British Drug Houses Ltd. (B.D.H. capillator), or as coloured disks mounted on a card from Mr. George T. Gurr of Fulham, S.W.6.

bacilli on microscopical examination, should be practically clear to the naked eye, unless there be turbidity due to phosphates. In favourable cases the improvement is indeed dramatic. If, however, these results are not obtained within a week or ten days from the time the urine first reaches a pH of 7.6, and provided, of course, that this reaction has been steadily maintained, it is extremely probable either that the original diagnosis was wrong or that some complicating factor is present and is keeping up the infection. Of the latter, in my experience, the most frequent are renal or ureteric calculi, congenital defects of the ureter, plugs of inspissated pus and cellular debris temporarily blocking the ureters or ureteric orifices, chronic ulceration with consequent distortion of the renal pelvis and calices, and incoordination of the neuromuscular mechanism of the renal pelvis, and of the vesical end of the ureters, as described by Hurst, Venables, and others. This last group I believe to be of more frequent occurrence than is usually supposed. But, whatever the cause, if an adequate response is not obtained as a result of treatment with alkalis within the period indicated it is important that time should not be lost, and at this stage it is wise to insist on further investigation by means of cystoscopy, ureteric catheterization, and possibly pyelography. I have seen the most serious consequences ensue from neglecting this rule and from procrastinating for any reason. I have the less hesitation in recommending this course from the knowledge that in the hands of an expert urologist the whole investigation can be carried out with very slight discomfort to the patient in his own home, unless pyelography be required, and without a general anaesthetic, which is usually both unnecessary and unwise. It may be objected that ureteric catheterization carries with it a danger of ascending infection. The risk is negligible, as under the circumstances for which the procedure is now advised there is already an infected tract on the defective side, whilst the unaffected is protected by an unusually copious stream of alkaline urine flowing down the ureter. There can be no doubt that the advantages to be gained by early urological investigation far outweigh the comparatively trivial, and largely theoretical, disadvantages.

After-care

When the patient has been up and about for some time on a normal diet cautious attempts may be made to reduce the dose of alkalis, but any return of pain, temperature, or turbidity of the urine must be met by a resumption of the former dose. Although the urine usually becomes quite clear to the naked eye in a very short time, microscopically a few pus cells, and especially bacilli, may persist in the urine for many weeks or months. It is important in such cases to continue with the optimum dose of alkali indefinitely, or until bacteriological investigations of catheter specimens of urine, repeated at intervals, give consistently negative results. In this manner alone is it possible to minimize the danger of relapses. I have had cases on 400, 500, and more grains of alkali per diem for periods of over two years in whom any attempt at reducing the dose was immediately followed by a return of signs and even symptoms. In the majority of cases, however, the infection dies out in the course of a few weeks or months.

Subacute and Chronic Cases

Although a considerable number of subacute and chronic cases are doubtless caused by inefficient treatment in the early stages strict alkali therapy should still be given a trial. If as a result an adequate response is not obtained in from ten to fourteen days of the urine attaining a pH of 7.6 then a complete urological investigation should be undertaken. Should no calculus, obstruction,

or mechanical defect be revealed, chronic ulceration of the renal pelvis should be suspected, and in all probability the case is incurable. In this event prolonged alkali therapy may be used with advantage for the prevention of acute exacerbations. It is important, however, to remember that there is a group of cases with chronic *B. coli* bacilluria without pyuria or other signs or symptoms of any kind and in which no evidence of mechanical obstruction or deformity of the urinary tract can be demonstrated. Such people lead perfectly normal and healthy lives for many years, and in my opinion, after a negative investigation for structural defects has been obtained, they are better off without treatment of any kind.

Alkalosis

There is fortunately no danger of alkalosis in uncomplicated cases of pyelitis because renal function is intact, and, under the regime outlined above, the volume of urine is so large that excess of alkali is rapidly eliminated. In most cases, therefore, a preliminary estimation of the alkali reserve of the blood is not necessary. Where, however, there is reason to suspect that the latter is above normal, preliminary investigation should be made before treatment is begun. Alkalosis is likely to be met with in cases with copious and intractable vomiting which has been present for some days, or when for any reason there is marked and prolonged dyspnoea. Under such circumstances alkali therapy must be instituted slowly and with care. Similar precautions should be taken when pyelitis is associated with chronic nephritis, especially with nitrogen retention. Care is also required in elderly subjects with gross cardiac irregularities. I have never seen clinical alkalosis result from giving adequate doses of alkalis in uncomplicated cases.

Lower Tract Infections

Infections of the lower urinary tract with *B. coli*—that is, cystitis, urethritis, vaginitis, etc.—are only mentioned here as, if associated with pyelitis, the urine may continue to be turbid, and to contain pus, albumin, and bacilli, long after the infection of the upper urinary tract has cleared up. It is therefore essential that catheter specimens of urine be examined from time to time, and occasionally it is necessary to test specimens obtained by catheterization of the ureters. It is not unusual for treatment to be continued much longer than necessary from failure to insist on the occasional examination of catheter specimens.

Pyelitis of Pregnancy

Acute and subacute *B. coli* pyelitis in pregnancy presents certain features peculiar to this state. At least in the later months of pregnancy some element of mechanical obstruction is probably always present, and this, of course, tends to increase as pregnancy advances. If the obstructive factor be marked then alkali therapy must inevitably fail. This is proved by the fact that cases not responding to adequate alkali therapy immediately improve after the insertion of indwelling ureteric catheters or on the termination of pregnancy. In early pregnancy, when obstruction, if present at all, is minimal in degree, thorough treatment with alkalis is to be recommended. In the later stages of pregnancy, with marked and increasing obstruction, alkali therapy is of doubtful value. It is under these circumstances particularly that a ketogenic diet, or mandelic acid, would seem to be indicated. Incidentally, it is of interest to note that in pregnancy, unless complicated by chronic nephritis, there is even less danger of alkalosis from the exhibition of large doses of alkalis, for in this state the kidneys are unusually permeable to alkaline salts.

Ketogenic Diet

The only other methods of treatment which deserve serious consideration are the ketogenic diet and its much more convenient offspring mandelic acid. There can be no doubt that in expert hands remarkably good results are obtained in a high proportion of cases. They are the only methods which successfully strike directly at the root of the evil by inhibiting the growth of the bacilli *in situ*. It is with no desire to belittle their value that I venture the following criticisms. Both acid and alkaline therapy call for some fortitude on the part of the patient, and scrupulous attention to detail is essential for success with either method. The most serious disadvantage of the "acid" methods is due to the impossibility of continuing treatment for sufficiently long periods to prevent relapses. The relapse rate is unfortunately high, and in fact many of the cases I have seen in the past two years have already had this treatment and have later relapsed. The method apparently offers little safeguard for the future. However, it is probable that a thorough urological investigation of these cases would have revealed mechanical conditions which are not amenable to this or any other form of medical treatment. It has already been stated that in the successful treatment of *B. coli* pyelitis the two essentials are correct reaction and adequate volume of the urine, and that the latter is by no means the least important. In treatment with "acids"—that is, ketogenic diet or mandelic acid—quite apart from the disputed question as to whether acids themselves in sufficient concentration, and over long enough periods, cause actual damage to the kidneys, it is necessary to induce a small volume of urine in order to obtain a sufficient concentration of acid to inhibit bacterial growth. This is effected by a rigid curtailment of the fluid intake. I believe that this in itself is harmful in these cases, and seriously militates against the success of these two methods of treatment. More hopeful would seem to be the use of some substance perhaps allied to mandelic acid but effective in an alkaline or neutral medium. So far as I am aware such a substance has not yet been found.

Conclusion

Alkaline therapy, on the other hand, possesses several distinct advantages, for it can be continued indefinitely without harm to the individual or serious interference with the activities of a normal existence; it permits of a normal diet being taken, and, above all, it confers protection against relapses so long as it is conscientiously carried out. Nevertheless it is of little use in cases with increasing urinary obstruction, as in the later stages of pregnancy, or in cases in which mechanical deformities of the renal pelvis or ureters cause stagnation of urine. It is of doubtful value, therefore, in cases with chronic ulceration and scarring of the renal pelvis, neuro-muscular incoordination, or congenital anatomical defects of the pelvis or ureters. Such cases can only be cured, if at all, by inhibiting the growth of the bacilli *in situ*, and it is in these cases, I believe, that the ketogenic diet or mandelic acid should be tried.

In conclusion, I would again emphasize the importance of adequate dosage and thorough and early urological investigation if medical treatment fails after, at most, two weeks' trial.

The method of treatment described was evolved during the course of investigations into the value of alkalis in the treatment of the various forms of Bright's disease, for which I received grants from the Medical Research Council and the Clinical Research Committee of Guy's Hospital. It is a pleasure to acknowledge my indebtedness to them.

CONTROL OF HAEMORRHAGE IN ENDOSCOPIC PROSTATIC RESECTION

WITH A NOTE ON CLOT RETENTION

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Haemorrhage in connexion with endoscopic resection of the prostate may be primary, reactionary, or secondary; in this operation primary and secondary haemorrhages are of more practical importance.

Primary Haemorrhage

Bleeding at the time of the operation can be a source of trouble in several ways. It obscures the operative field, necessitating frequent stoppages for lavage or coagulation, and thereby prolonging the operation unduly, or it may be so great as to compel the operator to stop altogether and resort to multiple sessions. It is also the most fruitful cause of accidents or mistakes, as was pointed out by Walker.¹ The actual blood loss is of itself rarely sufficient to produce serious exsanguination.

Excessive bleeding is to be expected from the resection of a large glandular prostate, especially one which has already given rise to haematuria, and if it were possible always to practise the operation which appears to be the best as judged by the local condition of the prostate these cases would be treated by suprapubic prostatectomy with closure, after the Harris technique. In discussing the selection of cases suitable for perurethral treatment the importance of the local condition of the prostate has been stressed by several writers.^{2 3 4} On the other hand, we cannot always practise what would be the ideal operation on local grounds, because there are many patients in whom the general condition makes prostatectomy extremely hazardous, or even entirely out of the question. To be able to include, safely and adequately, the "bad risk" case within the scope of the operation of endoscopic resection we must have some means of controlling the primary haemorrhage, whatever the local condition of the prostate may be.

Method of Control

Just as bleeding from an abdominal incision can be lessened by infiltration with a local anaesthetic containing adrenaline, so the same effect can be produced in the prostate. The only special instrument required is the long needle* illustrated in Fig. 1, which has been made for me by the Genito-Urinary Manufacturing Company. This is introduced through the channel in the electrotome designed for the coagulating electrode or through a separate mounting. A mixture of local anaesthetic and adrenaline is prepared beforehand. After experimenting with various concentrations I now use 0.5 c.cm. of adrenaline (1 in 1,000) added to 9 c.cm. of percarine (1 in 1,000); this is distributed under vision into the lateral and middle lobes of the prostate. In a considerable number of cases 1 c.cm. of adrenaline was used, but observations on a series showed that this produced a considerable rise of blood pressure, accompanied by tachycardia and pallor, though the blood pressure always fell again within a few minutes of the start of actual resection. When 0.5 c.cm. is used the rise in blood pressure is much less and the other effects are not so

* The instrument has recently been modified by the substitution of a detachable needle of the Schimmel type for the fixed point illustrated.