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B. COLI INFECTIONS: AETIOLOGY AND TREATMENT*

BY

D. M. LYON, M.D., D.Sc., F.R.C.P.Ed.

PHYSICIAN TO THE ROYAL INFIRMARY, EDINBURGH; PROFESSOR OF THERAPEUTICS AND CLINICAL MEDICINE IN THE UNIVERSITY OF EDINBURGH

The colon bacillus in the healthy individual is a harmless saprophyte, which possibly assists in the later stages of digestion. Under certain conditions it seems to be the organism responsible for infections in almost any part of the body. Inflammatory lesions in or adjacent to the alimentary canal are often due to this organism, and apart from these the sites most frequently affected are the urinary tract and the gall-bladder. In all cases the original source of the infection is doubtless the bowel, and much inquiry has been directed to the methods of spread to the secondary sites. The organism grows most freely in the caecum and ascending colon, where the contents of the bowel are still fluid, but the drier conditions in the lower colon are less favourable to it, and many die off. Some bacilli also exist in the lower ileum, though never in great numbers unless stasis be present. The neighbourhood of the duodenum is usually sterile. It was long believed that the healthy intestinal mucosa offered an effective barrier to the passage of organisms from the bowel. This does not seem to be strictly true, for several workers have confirmed the observation of Adami¹ that organisms may penetrate the wall of the bowel without causing any lesion during their passage. Doubtless lymphatic glands and liver serve as additional lines of defence. Warren and Whipple,² by x-ray application, destroyed the epithelium over large areas of the small intestine, and found that no massive invasion took place, though some organisms reached the neighbouring glands. Recent opinion suggests that a few organisms are constantly leaving the bowel, to be rendered harmless in the body.³

Infection of the Urinary Tract

There has been much controversy concerning the path by which colon bacilli may reach the urinary tract, but neither clinical nor experimental evidence is sufficient to give a conclusive answer. It is possible that under suitable conditions the organisms may pass by any of the paths suggested. Spread may occur by natural passages, by lymphatics, by the blood stream, or by a combination of these. At several points the alimentary canal and the renal system lie in close contact, separated only by a little connective tissue, and direct penetration may take place. In such situations lymphatic plexuses may offer a more ready path. There may also be invasion of the portal veins or of the general circulation by way of the thoracic duct. Ascending infection in the urinary tract is believed to occur along the lymphatics which surround the ureter. In females there may be direct spread across the perineum to the lower urethra, but upward extension along the lumen is usually considered

unlikely, even when gross obstruction exists.⁴ That urinary infection occurs more frequently in female infants at the diaper stage has been held to favour passage spread, but Nabarro⁵ has drawn attention to certain fallacies, and in any case the lesion appears most commonly in the right kidney before the bladder is involved. Most writers now seem to prefer the theory of blood spread to the kidney. If this be so, organisms circulating in the blood stream should reach other parts of the body, and should affect both kidneys equally, yet the right is involved much more frequently than the left. This theory also fails to explain why women are more liable to pyelitis than men.

Much experimental work has been done in trying to elucidate the problem. The feeding of large quantities of foreign *B. coli* to dogs resulted in the appearance of some organisms in distant tissues, and in the urine in three cases out of four.⁶ Direct injections into the blood stream have given information of rather negative value. The healthy circulation appears to possess an enormous protective capacity, for even when billions of organisms are introduced into a vein urinary infection may fail entirely,⁷ and the blood may be sterile within an hour.⁸ In similar experiments Book found that bacteria did not appear in the urine for many hours, and then only if local foci had been developed in the kidneys.⁹

Peritoneal injection of large quantities of *B. coli* culture result in a rapid appearance of the organisms in the blood stream,¹⁰ and some can be recovered from the urine within half an hour.¹¹ Thiele and Embleton¹¹ describe some interesting observations. They painted organisms in the anterior urethra of guinea-pigs, and found that they were rapidly conveyed by lymphatics to the capsule of the kidney and then by lymphatic paths to the general circulation. None were carried directly to the bladder. Reinfection of the body appears to occur readily from the urinary tract. Barrington and Wright⁸ investigated the blood before and after minor operations on the urethra. In a large percentage of cases slight trauma to the mucosa was followed by the arrival of organisms in the blood within a few minutes. The bacilli disappeared within half an hour.

Many observers have shown that the colon bacillus does not readily establish itself in the blood stream or in the urine in healthy animals. It would seem that factors other than the mere presence of the organisms are necessary for a lasting implantation.

Age and Sex Incidence

B. coli infections of the urinary tract may develop at any level from a urethritis to pyelonephritis and perinephric abscess. Pyelitis is probably the commonest

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lesion, while others are so mild as to suggest a bacilluria. Some writers consider these terms unjustified, and believe that there is always some underlying invasion of the kidney substance^{12, 26}; it should be remembered, of course, that only the more severe cases are examined by the pathologist. Urinary infections occur at any age, and are more frequent in females, both infants and adults. In males they are seldom found unless some obstruction is already present. When lesions affect different levels of the urinary tract the kidney is usually involved earlier than the bladder. Debilitating conditions, the presence of other disease, exposure to cold, fatigue, overexertion, starvation, undernutrition, and addiction to alcohol and drugs will undoubtedly favour infection by lowering resistance. These may affect either the bowel or the urinary tract.

Many practitioners have considered constipation and intestinal stasis important factors, but proof is difficult because of the frequent occurrence of these. Colitis, ulceration, diarrhoea, and the abuse of purgatives are equally important. Walker⁴ has proposed that a dose of cascara should be given to test whether a case of bacilluria has been completely cured. Such a dose will result in a reappearance of organisms in the urine if health has not been restored. No claim has been put forward that foreign bacteria in the bowel are more likely to gain entrance to the body. In the urinary tract the most important factor seems to be the presence of some obstructive lesion which interferes with free drainage. Experimentally this is also true, though the lesion may be very slight; obstruction of the urethra for as short a time as fifteen minutes may enable an infection to occur.¹³ In men enlarged prostate, stricture, and calculus favour infection, also nerve lesions such as tabes. Enforced rest after an operation, and unduly long retention of urine from any cause, are also said to be of importance. Mechanical causes, such as prolapse and external pressure, act in the same way. Pyelitis is common about the middle of pregnancy, and this may depend on the dilatation of the right renal pelvis, which is almost constant in this condition.⁴ The presence of foci in the gall-bladder or appendix may keep up a bacilluria.

Gall-bladder Infection

Infection of the gall-bladder may take place in much the same way as in the case of the urinary tract. Organisms may reach the liver by the systemic or the portal blood vessels, by lymphatics, and by the common bile duct. The bile, though alkaline, is an excellent culture medium for the colon bacillus and similar organisms. Typhoid bacilli are believed to reach the liver by the blood stream, and colon bacilli may arrive by the same path. Hurst¹⁴ has pointed out that where achlorhydria is present the contents of the duodenum are more alkaline—a condition favouring the growth of organisms—and retrograde infection of the biliary system is more likely in such cases. He also states that laparotomy, when followed by complete inhibition of gastric secretion and movement for a time, will allow *B. coli* to appear in the stomach within twenty-four hours.

In the gall-bladder the bacilli attack the walls, and so form a focus from which the bile can be constantly re-infected. As in the case of the urinary tract, the mere presence of organisms in the biliary system is probably not the only factor. Williams and McLachlan, studying the bacteriology of the gall-bladder, formed the impression that the *B. coli* and streptococci which were found were secondary invaders, enabled to settle down because of some toxic or chemical injury to the parts.¹⁵ The presence of gall-stones favours infection, and these depend to some extent on the occurrence of a high blood

cholesterol, though bacteria may also play a part in their formation. Anatomical abnormalities and mechanical faults leading to stasis or defective drainage of the gall-bladder are also of importance. Again, the presence of other foci of infection may predispose. Hurst reports that 37 per cent. of cases of cholecystitis had appendix scars.¹⁴

Septicaemia

Despite the apparent ease with which intestinal organisms invade the blood stream, true *B. coli* septicaemia is comparatively rare. Experiments already quoted have shown that even after massive infection the organisms fail to maintain themselves in the circulation. On the other hand, transient bacteraemia is probably very much more common than is usually supposed. Barrington and Wright have shown that organisms frequently reach the blood from the urethra if the urine is already infected⁸; Baird, who investigated the blood after labour, found coliform organisms within a few minutes of delivery, though they rapidly disappeared after an hour.¹⁶ He also draws attention to the danger of urinary infection in the puerperium from inability to pass water for some hours post partum.

As in the case of the local lesions, other factors appear to be essential for the development of septicaemia. It has been suggested that many cases of *B. coli* septicaemia may really be the overflow of bacteria from some local focus, such as the appendix or gall-bladder.

Treatment of *B. coli* Infections

A knowledge of the factors which permit an invasion of the body by the colon bacillus suggests measures which may be taken to prevent the infection: avoidance of debilitating and exhausting conditions, and the correction of all lesions which interfere with free drainage in the urinary and biliary systems. As the bowel is undoubtedly the original source of all infections, special attention should be directed to its proper functioning. Constipation must be corrected, but, in dealing with this, drastic purgatives must be avoided, as these carry fluid contents and more active organisms to the lower colon, and it has been shown that this may cause an exacerbation of the distant infection.⁴ Diarrhoea must be controlled, and other lesions of the bowel should be attended to.

The importance of such conditions is beyond doubt, but there may be other less obvious factors which favour invasion of the body. Colon bacilli isolated from distant lesions are usually of the same types as are commonly present in the alimentary canal, and it has not been held that foreign strains are more prone to cause infections. The importance of increased numbers of active *B. coli* in the small intestine or in the distal colon is more difficult to assess. In health the proportion of the various groups of organisms in the faeces is practically constant,¹⁷ but in certain conditions the stools may show an unusual preponderance of one or other type. Recognition of such abnormalities would warrant an attempt to correct them.

The so-called intestinal antiseptics are probably of little assistance, for in doses which are safe they cannot possibly sterilize the gut, and little is known of their effect on the various kinds of bacteria. Calomel in non-purgative doses is probably as useful a drug as any, and sulphur may also be of service. Many practitioners rely on preparations of liquid paraffin and agar for keeping the bowel in order. High colon lavage may be employed to get the lower bowel into a healthy state. An attempt may be made to alter the intestinal flora by implanting *B. acidophilus* and by giving lactose. Whole-wheat bread, uncooked starches—such as oatmeal—and sour meal preparations have been proposed for the same purpose.^{3, 18} There

is a certain amount of evidence that excess fat in the diet favours penetration of the bowel wall by organisms⁷; butter and eggs are therefore usually restricted. Almost all writers agree that milk should be avoided during the acute stages of renal infections, and meat is usually also restricted.

Measures to Raise Resistance

In dealing with *B. coli* infections bacteriological measures have not proved as satisfactory as might have been expected. This is probably due to the fact that the term "colon bacillus" does not represent one organism (as *B. typhosus* does), but includes some scores of different though closely related germs. Vaccine therapy has proved of service in the case of other infections, especially where the condition has become chronic, and benefit might be anticipated in the case of *B. coli* lesions. Opinions on this matter are very varied, and the usual belief appears to be that vaccines are seldom helpful. In view of this uncertainty it might be well to rely on autogenous preparations whenever possible.

Introduction of the bacteriophage has suggested interesting therapeutic possibilities. The interaction of phage and bacteria is so specific that it is unlikely that stock preparations can be of universal service. Few writers have claimed success in *B. coli* infections, and most have expressed doubt as to whether the method is worth the trouble it involves. Cowie¹⁹ gives a good account of the elaborate steps which are necessary to develop a satisfactory phage for each individual patient, but the results he reports seem to justify the special technique.

The bacteria of the colon group are said to produce two toxins—an endo- and an exo-toxin. Antisera have been produced against *B. coli* which are claimed to be both antitoxic and antibacterial.^{20,21} Even polyvalent sera can only be made against a few strains of organisms, and this probably explains why inconstant and unsatisfactory results are obtained.

Treatment of Urinary Infections

Some infections of the urinary tract are extremely mild and clear up spontaneously, others with tissue invasion and destruction may defy all attempts at cure. The majority lie between these extremes. For the acute phase treatment is standardized, but the chronic stages require individual measures. In acute cases the patient must be put to bed and kept uniformly warm. Large quantities of fluid should be given, together with alkalis, and perhaps an antispasmodic, such as hyoscyamus. Milk, meat extracts, and soups should be avoided; barley water, fruit juices, and glucose drinks should make up the fluid intake to three or four pints a day. Many writers suggest that copious flushing of the urinary tract is by far the best remedy for these infections.

By Administration of Alkalis

Alkalis are also very helpful in the early stages, and it has been stated that if alkali treatment were more efficiently carried out there would be fewer chronic cases.^{22,23} The colon bacillus can grow in media ranging from pH 4.4 to 9.4, and flourishes best between pH 6 and 7, a little to the acid side of neutral. Relief of symptoms may be obtained with relatively small doses of alkali which scarcely affect the pH, and even very large amounts of alkali can hardly raise the pH above 8,²⁴ at which value the organisms can still grow. The beneficial action has not been satisfactorily explained, since the change in pH hardly seems sufficient. The alkalis most commonly employed are potassium citrate and sodium bicarbonate up to 150 or even 300 grains of each in the twenty-four hours. One or more doses may also

be given during the night. These salts should be continued for several days after the temperature becomes normal, but they are apt to cause depression if kept up too long. It is often useful to have each specimen of urine tested with litmus paper to make certain that sufficient alkali is being given. In children, after the subsidence of symptoms, the urine should be kept mildly alkaline for weeks, and in pregnancy the alkalis should be continued to the end of term.

By Acidifying the Urine

When satisfactory administration of alkalis has not been successful in relieving the condition, the effect of acidifying the urine should be tried. Alternate periods of seven to ten days on alkali, and then on acid, may prove more successful than the continued use of either. The production of an acid urine is a necessary preliminary to the use of hexamine. Dilute acids are seldom used for this purpose, but acid sodium phosphate is usually employed. This salt will readily change alkaline urine, but it does not have much effect on a urine already acid. Ammonium benzoate is probably better, but it also fails to carry the acidity beyond the normal range. The acidifying chlorides of ammonium and of calcium act in a different way, and can produce a lower pH. They are apt to cause nausea and general upset, and a highly acid urine tends to irritate the urinary tract.

The Action of Hexamine

In trying to modify the reaction of the urine the character of the diet is of the greatest importance, for if the foods yield an alkaline ash extra acid will be required to overcome it. A large series of internal antiseptics have been prepared for sterilizing the urinary tract, but none is perfect. Disinfection of a healthy canal is comparatively easy, but organisms which have penetrated the walls of passages are beyond their action. Another difficulty is to attain a sufficient concentration of the drug in the urine. Of the urinary antiseptics hexamine is probably that most generally used. It acts by liberating formaldehyde, a change which takes place only in an acid medium. A solution of 1 in 5,000 is bactericidal, but such a concentration is probably never attained in the urine. It is doubtful whether 1 in 20,000 is often exceeded, and at such a concentration the growth of *B. coli* would only be inhibited. In addition, some of the drug is probably decomposed in the gastric juice, especially if it is given after meals. Acid-forming salts must be given at a sufficient interval from the hexamine, so that interaction will only occur in the urine. The combination of antiseptic and acid urine may be very irritating in the urinary tract, and this treatment must be avoided in acute infections, since haematuria or even strangury may be produced. In an alkaline urine the hexamine is excreted unchanged. It is interesting to note that certain writers believe that here, as in the alkaline bile, hexamine can benefit the patient in some other way than by producing formaldehyde. Some *B. coli* infections clear readily with hexamine and an acid urine, but lesions in the kidney and renal pelvis are less easily controlled, as little formaldehyde may be evolved at this level. Failure with hexamine is undoubtedly due to the difficulty in obtaining a sufficient concentration of the antiseptic.

Hexyl-resorcinol is said to be germicidal in either acid or in alkaline urine. It has a remarkable effect in rapidly clearing up coccal infections of the lower urinary tract, but in other respects it is not better than other antiseptics.²⁴ *B. coli* infections may require months of treatment where other organisms disappear in a short time. The fluid intake should be restricted during the

use of this drug, to increase its concentration in the urine.

Dyes of the pyridine series have recently been employed as urinary antiseptics. They also can be used without regard to the reaction of the urine, and it is claimed that they can penetrate the walls of the tract and so exert an antiseptic action in the tissues. The flavine series have been used by mouth, intravenously, and for local irrigations. They have the advantage that their action is not impaired by the presence of serum. Euflavine is probably the best of the group, the urine being made alkaline with sodium bicarbonate. In chronic cases a succession of such remedies can be tried. Attention must be directed to possible foci of reinfection, and any factor which may cause stasis or retention must be dealt with. In certain cases, as in pregnancy, the indwelling ureteral catheter is of temporary advantage.

The Ketogenic Diet

The observation that the urine of diabetics with acidosis and of epileptics under the ketogenic diet did not readily become infected suggested the use of this type of diet in cases of urinary infection. To produce the appearance of ketone bodies in the urine a very strict dietary control is essential. The diet contains large quantities of fat, and the carbohydrate has to be restricted to between 20 and 30 grams. After a few days on this strict regime acetone bodies begin to appear in the urine, and the pH may fall to about 5. Tested on a group of chronic cases which had resisted all other forms of treatment, this method proved successful in about one-half the patients, the infection clearing up in remarkable fashion in some of the cases.²⁵ The ketogenic diet is unappetising and even nauseating, and it is difficult to get patients to co-operate thoroughly for any length of time. It is unlikely that this method of treatment will be much used except in the most resistant cases.

Biliary Infections

The effects of treatment in lesions of the biliary tract can be less easily observed than in the case of the renal system. During the acute phase general measures must be taken against pain and fever. For chronic infections, where surgery is not indicated, other medical methods may be tried. As in the case of the urinary tract, an effort should be made to flush the system. A copious intake of fluid may be helpful in producing a free flow of bile. Drainage of the gall-bladder and biliary passages may be regularly undertaken by introducing concentrated magnesium sulphate through a tube in the duodenum. Specimens of the bile can be withdrawn and examined bacteriologically if care be taken to avoid contamination, but the results so obtained are not very reliable. Hurst¹⁴ finds that magnesium sulphate by mouth (without the tube) is just as efficient. He gives each morning the largest dose of a concentrated solution which the patient can take without being purged. The action may be further enhanced by an injection of pituitrin a quarter of an hour before taking the Epsom salts. Half an ounce of olive oil before meals may stimulate a flow in the same way. Treatment can be reinforced by the administration of sodium salicylate or hexamine; the salicylate is an efficient cholagogue. Hexamine reaches the bile, and is frequently prescribed in conditions of the gall-bladder, but as the medium is alkaline it is difficult to see how it can act. Hurst says that it can clear up an infection in a few days.

In *B. coli* septicaemia a search should be made for a focus of infection which may be constantly passing organisms into the circulation. Intravenous medications are of doubtful value. Mercurochrome has been most often given, but it is not without danger.

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CONDITIONS PREDISPOSING TO B. COLI INFECTION AFTER POST-OPERATIVE RETENTION*

BY

CUTHBERT DUKES, M.Sc., M.D.*

PATHOLOGIST, ST. PETER'S HOSPITAL; DIRECTOR OF RESEARCH
LABORATORY, ST. MARK'S HOSPITAL

The *B. coli* infections of the urinary tract which follow post-operative retention can be studied with a completeness which is not possible in sporadic infections. Tests can be carried out before the operation to find if the urinary organs are healthy, and periodic examinations during convalescence will show at what time and in what circumstances the urine becomes infected. The observer is in the fortunate position of knowing when the patient will be exposed to the risk of infection: he can look for common factors in those who succumb and those who escape.

During the last six years I have had the opportunity of making daily observations on 214 cases of retention of urine following the operation of excision of the rectum for cancer. This operation does not open or directly damage the urinary tract, but like other extensive pelvic operations it disturbs the nervous mechanism of micturition, necessitating catheterization usually for three or four days. In many of these cases urinary sepsis supervenes, the infection being attributable either to instrumentation or to a lymphatic or haematogenous infection from the operation wound. Other patients escape infection. We are discussing the aetiology of *B. coli* infections to-day, and my contribution consists in a demonstration of those conditions which predispose to infection when the function of the bladder is temporarily deranged after surgical operations.

Incidence of Infection

It will help towards an understanding of the question if before describing the factors which predispose to infection in this type of case I mention some which do not

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