which were the cause of the high blood pressure; the feeble and more empty radial artery, instead of meaning lessened output, may be accompanied by greater efficiency of the circulation and an increase in the cardiac output.

In the brachial artery, when a sphygmomanometer is used really valuable information as to the cardiac output is obtainable if the range of oscillation of the needle of the aneroid be studied as well as the systolic and diastolic pressures. An abnormally small range of oscillation naturally implies a deficient distension of the arm with blood at each beat of the heart, and therefore presumably a lessened output. It is often possible by the use of the sphygmomanometer alone to diagnose cardiac inefficiency such as that which follows influenza, and to forecast with fair accuracy what other signs of deficient output will be observable in the patient. It must, however, be remembered that in certain conditions small oscillation of the pulse does not imply diminished cardiac output, but only an abnormal state of the peripheral circulation. For instance, a small range of oscillation usually characterizes Graves's disease, Ménière's vertigo, and allied conditions. Information as to the cardiac output can also be gained by noting the nature of the sound heard at the bend of the elbow when using the auscultatory method of reading the blood pressure. A distinctly slapping sound is suggestive of badly filled arteries, due either to failure in cardiac output or to undue relaxation of the arterial system.

When knowledge of the sphygmomanometer has been further increased it is possible that valuable information as to the cardiac output may be given by the relation of the systolic pressure estimated by the finger to that estimated by auscultation, taken in conjunction with the information given by the range of oscillation of the needle of the aneroid.

On comparing the information gained by observation of the size of the lungs, of the physical condition of the liver as judged by percussion, together with the size of the area of cardiac dullness and the results given by the sphygmomanometer, a very trustworthy and exact estimate can be formed as to cardiac output, and the recognition of myocardial weakness will be made more easy, whether toxic in nature or due to atheroma of the coronary arteries. It must, however, be borne in mind that the cardiac output may be lessened by the compensatory diminution in the total volume of blood in circulation which occurs (apart from cardiac weakness) in starvation and certain other pathological conditions.

REFERENCE.

¹ See *The Early Diagnosis of Heart Failure*, Figs. 42 to 45 (pp. 196-199).

URINARY INFECTIONS WITH *B. COLI* AND THE PYOGENIC COCCI:

THEIR PATHOLOGY AND THEIR TREATMENT WITH COLLARGOL.

BY

HAROLD H. SANGUINETTI, M.D., B.Ch.,
PATHOLOGIST, LONDON TEMPERANCE HOSPITAL.

A THOUSAND years ago Rhazes¹ described a case of urinary infection in a young man, but it was not until, at the fifteenth French Congress of Surgeons in 1892, Guyon and Reblaub² called attention to the frequent occurrence of spontaneous urinary infections—that is, infections not resulting from trauma or consequent on obstruction—that medical men became alive to their existence. Guyon then expressed the view that the infection was an ascending one from the bladder to the kidney, but ever since there has been a controversy about this question, concerning which there are now two main views.

The first view, the one enunciated by Guyon and vigorously supported by C. R. Box³ among others in this country, maintains that the infection passes from the external surface of the urinary organs along the urethra to the bladder and thence upwards to the kidneys; while according to the second view the infection is haematogenous, and first affects the kidney and its pelvis, whence it passes down into the bladder. Frank Kidd is a firm upholder of

this view, which is accepted by Sir William Hale-White⁴ and probably by the majority of physicians and surgeons. Of course, the fact of the infection being haematogenous would not preclude primary infection of the bladder with ascent to the kidney. The upholders of the ascending view lay stress on the far greater frequency of the complaint in females than in males, while their opponents point out that, although less frequent than in females, cases of urinary infection are quite common in males, in whom the length of the urethra renders the probability slight of an infection spreading from the meatus to the bladder, even if contamination with the most common infecting organism, the *B. coli*, were more frequent than it probably is. Experimental evidence of the effects of the presence or absence of obstruction is adduced in favour of their argument by both sides. Frank Kidd⁵ maintains that "Pure cystitis seldom occurs, but when it does it is never associated with fever. This is because the bladder is designed as a reservoir, is poorly supplied with lymphatics that it shall not absorb water, and therefore equally not poisons."

Now the line of treatment adopted must depend on which of these views is correct. In the end we shall probably find that both views are correct—that is, that in some cases the infection starts in the bladder, in others in the kidney, and that naturally a different line of treatment will be needed for each class of infection. L. S. Dudgeon⁶ and his co-workers showed that in 74 per cent. of *B. coli* infections in females a non-haemolytic bacillus was present, a haemolytic type in 26 per cent., while in males this order of frequency was reversed. This lends some support to the view that the usual progress of the infection differs materially in the two sexes.

The protagonists of both views regard the symptoms of fever, general malaise, and tenderness over one kidney as always evidence of the existence of pyelitis, but I question whether this view is based on indubitable evidence. Cystoscopy combined with urethral catheterization might give the evidence desired, but in the early stages such examinations are considered inadvisable. However, Frank Kidd has made two or three cystoscopic examinations in the earliest stages, and thus describes what he saw:

"The whole bladder wall was intensely engorged and inflamed, and covered with portions of purulent membrane or fibrinous deposits and the mouths of the ureters buried in the general oedema of the mucous membrane."

I suggest that such oedema produces partial obstruction of the ureteric orifices with consequent distension of the ureter and renal pelvis, accompanied by congestion and tenderness of the kidney. I do not maintain that the pelvis of the kidney is never involved in these cases of urinary infection, but question whether the involvement is as frequent as is usually maintained.

From the successful effects of renal lavage, in which 4 c.cm. of 5 per cent. collargol are injected through a ureteric catheter into the renal pelvis, compared with the unsatisfactory results of ordinary vesical lavage, Frank Kidd considers he has clinched the argument in favour of primary, and persistent infection of the kidney, into which he has found the collargol penetrates. In view of the results I have obtained by injecting 0.5 to 2 per cent. collargol into the bladder, I am led to doubt whether his conclusions are justified. It must be borne in mind that 4 c.cm. of 5 per cent. collargol would make 40 c.cm. or about 1½ oz. of 0.5 per cent., and that the results attributed to renal lavage may possibly be due to the effect of the collargol on the bladder. I must, however, admit that I have obtained no such striking successes as cure after two or three injections. However, in Case 1 of my series the patient, who, previous to receiving the treatment I will describe, suffered from recurring attacks of fever, after treatment had no more of such attacks and has remained cured for over four years. It seems reasonable to conclude either that cystitis alone may produce all the symptoms usually attributed to the presence of pyelitis, or that pyelitis in this case was the result of an ascending infection. The other successful cases of this form of treatment justify the conclusion that, whether the infection ascends or descends, infection of the bladder alone is a very frequent condition in chronic cases, and that, even if the acute cases start in the renal pelvis, the infection there soon disappears, while that in the bladder

persists. Even cases of bacilluria have been cured by intravesical treatment.

In treating these infections a drug must be chosen which, while it may have a direct bactericidal effect *in vitro*, must not impede, and, if possible, should stimulate the natural methods of the tissues in overcoming infection. Collargol appears to possess these qualities.

Collargol, first used in the treatment of cystitis by Voelker and Lichtenberg⁷ in 1905, was recommended to me for the treatment of a *B. coli* urinary infection by Mr. Percy Sargent in 1912. But although its beneficial action was reported so long ago, and although Frank Kidd speaks highly of its use in renal lavage, little use seems to have been made of it in recent years, partly, no doubt, owing to the unfavourable report on its bactericidal action by Marshall and Neave⁸ in 1906, but mainly owing to the prevailing view that the primary and persistent seat of the infection was the kidney and renal pelvis. I have, however, myself investigated the bactericidal action of collargol *in vitro*, and found that in a dilution of 0.25 per cent. it will destroy *B. coli* in half an hour (a very conservative estimate of its potency), and that it is equally efficacious against streptococci. But its action in these infections is due not only to its bactericidal action, otherwise a 4 per cent. solution, which is quite well borne by the bladder—that is, can be retained without discomfort—would produce the best effects, whereas it will be found that 0.5 to 1 per cent. will usually prove more efficacious. The strength must be controlled by microscopical examination, and in the early stages pus must be regarded as beneficial and not the reverse. Indeed, in a case of bacilluria no progress can be looked for until pus cells begin to appear in the urine. When a case, after progressing favourably, tends to relapse, then usually it will be found advisable to reduce the strength of the collargol solution injected.

The technique of the treatment is simple, and in females can be carried out by a well trained surgical nurse, but unless sure of the nurse's skill the medical attendant should carry out the treatment himself. One of the two men in my series of cases carried out the later part of his treatment himself. A syringe, such as the ordinary large metal ear-syringe with a conical nozzle, capable of holding 2 to 3 ounces, is filled with the collargol of the desired strength (0.5 per cent. is a good strength to begin with, sterile water being used as a diluent); see that the syringe does not leak at the junction of nozzle and barrel. A soft rubber or gum-elastic No. 8 catheter with a conical proximal end, into which can be inserted the nozzle of the syringe, is passed into the bladder with aseptic precautions. Any urine in the bladder is drawn off and a sample kept for microscopical examination. The nozzle of the syringe is now inserted into the catheter and the collargol injected, after which the catheter, still attached to the syringe, is withdrawn, the collargol being allowed to remain in the bladder until the patient feels a desire to void it—that is, from twenty to sixty minutes. A small glass funnel, into which the collargol can be poured, may be substituted for the syringe. As the collargol solution is brownish-black and cannot be easily removed from any fabric on which it drops, care must be taken suitably to protect the bedclothes, etc.

It is not necessary for the patient to remain lying down after the injection, nor to remain in bed during the course of treatment, but confinement to bed will probably hasten cure, and in resistant cases should be insisted on. Injections are made daily until the urine, as shown by microscopical and cultural examination, has become sterile, or until success by this line of treatment seems improbable.

The number of cases—namely, 17—treated by me is possibly too small to base an optimistic estimate of the results obtainable if the treatment were more widely used, but it has enabled me to follow the urinary changes with the microscope, in many cases by daily examinations.

The 17 cases treated by me since 1921 were infected at the outset with the following varieties of bacteria: 2 cases with staphylococci only; 2 cases with *B. coli* and streptococci; 2 cases with *B. coli* and staphylococci; 11 cases with *B. coli* only. Eleven cases have been cured, in the sense that at the end of treatment neither pus nor bacteria were present in the urine, as proved by microscopical and

cultural tests. In 7 of these the urine was known to have remained sterile for at least a month. It was not possible to keep the remaining 4 patients under observation so long. Case 4 in the series has had three attacks, each of which has been successfully dealt with, the urine having been rendered sterile on each occasion for lengthy periods. There has, then, been a successful result in 64.7 per cent. of the cases, or, if Case 4 be counted as three cases, in 68.4 per cent.

Case No.	Sex and Age.	Private or Hospital	Duration of Infection Prior to Collargol Treatment.	Organisms Present.	Length of Collargol Treatment.	Result.
*1	M. 50	Private	6-7 years	<i>B. coli</i>	Not known	Cured.
*2	F. 40	Private	Few days	<i>B. coli</i>	14 days	Cured.
3	F. 48	Private	2 months	<i>B. coli</i>	2 periods of 3 weeks	Not cured.
*4	F. 47	Private	6 or more years	<i>B. coli</i>	1st attack 14 days;	Cured.
					2nd attack 19 days;	Cured.
					3rd attack many weeks	Cured.
5	F. 40	Private	5-6 days	<i>B. coli</i>	9 days	Cured.
*6	F. 83	Private	1 month	<i>B. coli</i> and staphylococci	56 days	Cured.
7	F. 18	Hospital	4-5 weeks	Staphylococci	10-14 days	Cured.
*8	F. 35	Private	5½ years	Streptococci and <i>B. coli</i>	16 days	Cured.
*9	F. 65	Private	3 years	<i>B. coli</i>	12 days	Cured.
10	F. 65	Hospital	? 5 years	<i>B. coli</i>	15 days	Not cured.
11	F. 43	Hospital	1 month	<i>B. coli</i>	3-4 weeks	Not cured.
12	F. 41	Hospital	?	<i>B. coli</i>	14 days	Cured.
13	F. 33	Hospital	1 week	<i>B. coli</i> and staphylococci	1 month	Not cured.
14	F. 47	Hospital	13 months	<i>B. coli</i> and streptococci	10 weeks	Not cured.
*15	F. 49	Hospital	? 3 years	<i>B. coli</i>	1 month	Cured.
16	F. 66	Private	? years	<i>B. coli</i>	16 days	Cured.
17	M. 53	Private	? years	Staphylococci	14 days	Not cured.

* In these cases freedom from infection was known to have lasted at least a month. Case 10 had a relapse three weeks after leaving hospital, where too late she was found before her discharge still to have slight urinary infection. Case 13 was practically free from infection on discharge from hospital. The hospital cases, owing to operations and other causes, were usually not in as good general health as the private cases.

Unless treatment is continued until the urine is free from pus and sterile relapses are liable to occur. Macroscopic examination is certainly not sufficient, nor do I think we may be content with microscopical examination. Cultural tests are almost essential, although, in the case of a *B. coli* or streptococcal infection, the development of three or four colonies of *Staphylococcus albus* on the culture medium may indicate no more than infection from external parts during the passage of the catheter.

The following is a list of the cases with a very brief summary of the course of treatment.

Case 1.—F. A. N., male, aged 50. *B. coli* infection followed two months after operation by Sir John Thomson-Walker for removal of calculus from left ureteric orifice. Treated by various means, including vaccines and lavage, until 1921. Had several attacks of fever. Early in 1921 began treatment with 2 per cent. collargol. Improvement rapid, but exact time required to render urine sterile not known, as after the first few injections the patient administered the remaining injections himself. Has remained cured four years.

Case 2.—Mrs. G. *B. coli* infection with fever during convalescence from hysterectomy. Collargol 2 per cent. injections cured the condition in about fourteen days. Urine sterile three to four weeks later.

Case 3.—Miss N. Severe attack of pyelonephritis. Temperature 103° to 104° F. Pus and *B. coli*. Treated with potassium citrate and later with vaccines. Two months after attack collargol 2 per cent. injections begun. Treatment at first greatly improved condition of urine, but success was not maintained and treatment was discontinued. (Better results might have been obtained by reducing the strength of collargol.)

Case 4.—Mrs. N., aged 47, wife of Case 1. Had suffered from *B. coli* infection six years. Had *B. coli* bacilluria when treatment by collargol 2 per cent. was begun. Improvement began when collargol 1 per cent. was substituted. The urine then became sterile in fourteen days. Has subsequently had two reinfections very resistant to treatment, but was ultimately cured.

Case 5.—Miss B., aged 40. *B. coli* infection with frequent painful micturition for five to seven days. Temperature 99.4° F. Collargol 2 per cent. rendered urine free from pus and organisms in nine days.

Case 6.—Mrs. K., aged 83. Attack of fever suggesting influenza or appendicitis. Temperature 101° F. Pus, *B. coli*, and staphylococci in urine. Temperature normal three weeks after beginning of attack. Ten days later collargol injected. Urine not sterile till fifty-sixth day of treatment. Injections almost, but not quite, daily, the strength of collargol varying from 0.5 to 2 per cent. and even 4 per cent., but strong solutions made matters worse. Urine sterile many months after cessation of treatment.

Case 7.—Mrs. M., aged 18. Staphylococcus infection. In-patient in London Temperance Hospital for three weeks. Treated with oral administration of drugs. Collargol injections in out-patient department produced cure in ten to fourteen days.

Case 8.—Miss E., aged 35. Urine infected with streptococci and *B. coli*. Collargol 1 per cent. cured the condition in about a month.

Case 9.—Mrs. T., widow, aged 65. Cystitis since removal of an innocent intravesical growth in Guy's Hospital three years previously. Frequent micturition, pus, and *B. coli*. Collargol 1 per cent. injections. Urine free from pus and sterile after nine days' treatment. Treatment discontinued on the twelfth day; urine still sterile on the seventeenth day, and no return of symptoms up to time of her death from pneumonia six months later.

Case 10.—Woman, aged 65; in-patient in London Temperance Hospital. First had difficulty in micturition in 1918; cured April 12th, 1923. On April 19th painful micturition, pus, and *B. coli* in urine. From April 30th till May 14th collargol 1 per cent. daily. On June 15th only four colonies of staphylococci on agar inoculated with loopful of deposit. On May 23rd culture revealed a few staphylococci and *B. coli* in urine. She had no further treatment and was discharged. Three weeks later reported by medical attendant to have another attack of "cystitis."

Case 11.—Married woman, aged 43; in-patient in London Temperance Hospital. Hysterectomy, April, 1923. Just prior to operation urine "strong-smelling." On May 1st the urine contained pus and *B. coli*. Collargol 1 per cent. given for three to four weeks without much improvement. (Twelve months later no pus in urine, three or four colonies of *Staphylococcus albus* developed from loopful of deposit.)

Case 12.—Woman, aged 41; in-patient in London Temperance Hospital. Pus and *B. coli* in urine. Collargol 1 per cent. injections rendered urine sterile in approximately fourteen days.

Case 13.—Married woman, aged 33; in-patient in London Temperance Hospital. Febrile attack; pus, *B. coli*, and staphylococci in urine. On the tenth day, when the temperature had fallen to normal, collargol injections begun. Strength varied from 0.5 to 2 per cent. A month's treatment had not rendered the urine quite sterile, nor free from pus cells.

Case 14.—Married woman, aged 47; in-patient in London Temperance Hospital. Frequent painful micturition ten months prior to operation for a large uterine fibroid, which was followed by phlebitis. Urine examined two months after operation contained blood, pus, *B. coli*, staphylococci, and diphtheroid bacilli. Collargol injections persisted in for about ten weeks, with one or two intermissions, resulted in considerable improvement, but not cure.

Case 15.—Married woman, aged 49; in-patient in London Temperance Hospital. Operation March 27th, 1924—amputation of uterine cervix, colporrhaphy and perineorrhaphy. Had discomfort in bladder for three years. On April 14th much pus and *B. coli* in urine. On April 19th injections of collargol begun and continued till May 12th, when neoprotosil 10 per cent. was substituted for the collargol. Treatment discontinued on May 15th, and patient discharged from hospital on May 22nd, when no *B. coli* were present in the urine.

Case 16.—Mrs. H., widow, aged 66. Had synovitis with effusion in left knee. Urine contained pus and *B. coli* (condition probably of long standing). No urinary symptoms. Collargol 1 per cent. injections rendered urine sterile in seventeen days. Sterile a month later.

Case 17.—M. de L. Long-standing urinary infection. At beginning of treatment blood, pus, and staphylococci present in urine in considerable quantity. Collargol 0.5 per cent. injections rendered urine sterile in twelve days. Bacteria but no pus present one week later.

While very well satisfied with the results I have so far obtained with collargol, and convinced of its efficacy, I do not suggest that equally good results might not be obtained with other remedies unused by me. Certainly the ordinary antiseptics used for lavage have not proved curative. What, however, I desire most to suggest to my medical brethren is, not the efficacy of any particular drug, but the efficacy of treatment of these infections through the bladder.

In conclusion, I desire to express my thanks to my colleagues Mr. James McClure and Mr. R. A. Kerr for permission to treat cases under their care in the London Temperance Hospital, and for their friendly encouragement during the course of the investigations. My thanks are also due to Messrs. John Bell and Croyden, Ltd., for greatly assisting me by obtaining for me a supply of collargol at a cost much below the usual market price.

REFERENCES.

¹ E. G. Browne: *Arabian Medicine*. ² *Proceedings of 15th French Congress of Surgeons*. ³ C. R. Box: *Lancet*, January 11th, 1908. ⁴ Sir William Hale-White: *Ibid.*, June 24th, 1908. ⁵ Frank Kidd: *Common Infections of the Kidney*. ⁶ L. S. Dudgeon, E. Wordley, and F. Bawtree: *Journ. of Hygiene*, November, 1922, pp. 168-198. ⁷ Voelker and Lichtenberg: *Muench. Med. Woch.*, 1905, No. 33. ⁸ Marshall and Neave: *BRITISH MEDICAL JOURNAL*, August 18th, 1906.

A CLINICAL STUDY OF RHEUMATOID ARTHRITIS.*

BY

A. H. DOUTHWAITE, M.D., M.R.C.P.

THE following observations are based on examination of 50 patients suffering from rheumatoid arthritis, 38 of whom were females. Attention has been purposely directed more to the patient's general condition than to the state of the affected joints, which are only too apt, by their prominence, to absorb the interest of the physician to the detriment of the patient. Thus in every case, prior to the onset of joint pain, there had been a period, extending in one case up to two years, during which a gradual deterioration of health was in progress. This showed itself most frequently by loss of energy, both mental and physical, together with constipation, and loss of weight and appetite. In a few cases increasing pigmentation of the skin, so typical of this disease, had actually been observed before any painful symptoms had arisen.

No direct relationship could be traced between general diseases contracted in earlier life and the occurrence of rheumatoid arthritis. In 20 per cent. of cases there had been, however, an illness shortly preceding, and probably precipitating, the onset of the disease—a fact which goes to prove that an attack of rheumatoid arthritis is almost invariably dependent on a previous lowering of the general bodily resistance. Of these, influenza occurred in 8, bronchitis in 1, puerperal haemorrhage in 1.

ONSET OF ARTHRITIS.

It is of great importance to note that in no case was more than one joint involved in the original attack. This was usually the wrist or one of the interphalangeal joints, which, having remained swollen and painful for a few weeks, completely subsided. This was followed, after any period from a few days to several weeks, by extension to other joints.

Particularly noteworthy are those symptoms referable to the involvement of the small joints of the spine and the neighbouring structures. Pain radiating over the occiput may be the very first symptom—in fact, 4 of my cases were originally sent to neurological out-patient departments, 2 diagnosed as neuralgias of obscure origin, and 2 as functional headache. The patients themselves may refer to this pain as headache, but actually it is quite distinctive, being frequently unilateral, intermittent and shooting in character, aggravated by rotation of the head, and following the course of the occipital nerves. When changes occur in the superficial joints, the diagnosis of this pain is clear, but before this it can only be suspected by exclusion, for changes demonstrable by the x rays, though usually present in the later stages of the disease, cannot be looked for during the first few months. Girdle pains may be produced in like manner by involvement of the intercostal nerves.

Considerable difference of opinion exists as to the correct explanation of these symptoms. That the pain should be due to any pressure by bony outgrowth is inconceivable, for this does not occur, at any rate for several years. There are, then, two hypotheses left: one is that there is a direct infection of the nerve roots by the same process that gives rise to the arthritis; the other, that the nerve root is compressed by inflammatory swelling of the involved connective tissue in the joint neighbourhood, or that the inflammation extends directly into the nerve roots. Arguing on the analogy of the more superficially placed joints, the latter view is perfectly tenable, for indeed their early deformity is largely due to periarticular swelling. Furthermore, the nerves which are involved are usually those related to a diseased area of the spine—a fact which suggests a localized inflammatory process rather than one attacking them independently via the blood stream.

Skin.—The skin is moist, profuse sweating being present on the legs, feet, and palms of the hands. The discoloration of the skin, so admirably described by Kent

* Thesis approved for the degree of Doctor of Medicine in the University of London (abridged).