THE CHEMOTHERAPY OF TUBERCULOUS INFECTIONS OF THE URINARY TRACT

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In considering the effects of chemotherapy on tuberculous infections of the urinary tract, the nature of the lesion responsible for the infection must be borne in mind. A tubercle positive urine denotes the presence of a kidney focus or foci whence the organisms emanate. It follows that the aim of chemotherapy when employed for the treatment of this disease is not merely to render the urine tubercle negative; the objective must be the healing of the diseased kidney which otherwise will continue to act as a source of infection. Renal tuberculous lesions are encountered in infinite variety, from microscopic symptomless foci to solitary or multiple, ulcerative or caseo-cavernous excavations, which may ultimately riddle the organ. There may be clinical involvement of both kidneys, the disease in that event usually being more advanced on one side. A factor of fundamental importance in its bearing on treatment is that renal tuberculosis is not a local disease, but is a blood-borne focal manifestation of a systemic infection generally commencing in the chest, less often in the gastro-intestinal tract. The extra-urinary lesions may or may not be clinically active when the renal disease is recognized.

Streptomycin is regarded as the most potent antibiotic that is at present available for the control of urinary tuberculosis, and the main purpose of this article is to indicate what may be expected from its employment in this connection. The results obtained at Robroyston Hospital, where a controlled trial, which commenced three years ago under the auspices of the Tuberculosis Research Unit of the Medical Research Council and still continues, provide the source of the information that follows.

Streptomycin

The trial at Robroyston has up-to-date included 130 patients, of whom 67 have been given streptomycin and 63 have been designated as controls. The selection is made from a sequence of numbers taken from a statistical list at the

M.R.C. office. The patients treated by streptomycin are given $\frac{1}{2}$ gm. twice daily by intramuscular injection, with accompanying alkalinization for 90 days. Controls and those streptomycin-treated receive similar general medical care, and comparative results are assessed by a routine mode of investigation on every patient. This includes examination for tubercle bacilli in the bladder urine by direct smear, guinea pig inoculation and culture, and on all possible occasions the separate kidney urines are similarly tested. Cystoscopic and pyelographic (excretory and retrograde) examinations are made before and after treatment and during the follow-up period. In order to facilitate the assessment of results patients are placed in one of the following five clinical categories:—

Group 1. Unilateral renal tuberculosis—minor lesion without cystitis.

Group 2. Unilateral renal tuberculosis—major lesion necessitating nephrectomy; cystitis.

Group 3. Bilateral renal tuberculosis—nephrectomy for the more advanced lesion.

Group 4. Tuberculosis occurring in the remaining kidney subsequent to nephrectomy for unilateral disease.

Group 5. (a) Major bilateral tuberculous lesion (b) Minor bilateral tuberculous lesion.

These groups include every type of renal tuberculosis excepting those suffering from tuberculous bacilluria without a demonstrable renal lesion, and those with clinical unilateral lesions who become tubercle-negative after nephrectomy. The exclusion of these two varieties from the investigation is of importance in a comparative study of the reported results from other centres.

In this article it is proposed to summarize the results of treatment obtained in the respective groups, a statistical report on the first 90 patients having previously been made (Jacobs and Borthwick, 1950).

Group 1. In this group with minimal unilateral pyelographic changes, the urine of the strepto-

mycin-treated patients become tubercle negative more frequently than those of the controls undergoing the routine sanatorium regime. A reversion to a tubercle-positive urine is, however, usual within a few months of completing the course. It has also been found that the administration of streptomycin does not prevent the appearance of a tubercle positive urine from a previously negative contralateral kidney. The pyelographic studies indicate that occasionally the focus may become temporarily walled off. The focus itself remains active, as has been proven by nephrectomies or partial nephrectomies carried out on a number of these patients at varying intervals after treatment has ceased.

Group 2. Conversion of urine to tubercle negative after nephrectomy occurs in a significantly higher percentage of the streptomycin-treated patients suffering from a major unilateral lesion with secondary cystitis. A corresponding improvement in the secondary cystitis generally takes place. If, however, the cystitis is already well established and the bladder capacity seriously reduced prior to the commencement of the treatment, streptomycin may aggravate the contracture, even though the urine becomes tubercle negative.

Group 3. Patients in this group have a bilateral renal infection, well advanced on one side and of a minor degree on the other. Following removal of the kidney which is the seat of the more major lesion and streptomycin treatment, a significant conversion from tubercle positive to negative is obtained. This happening is usually temporary and is directly related to the state of the lesion in the remaining kidney, the conversion tending to occur only when the original pyelographic changes are insignificant. A well-defined lesion continues to progress and the urine remains positive in spite of treatment.

Group 4. These patients have developed disease in the remaining kidney subsequent to a nephrectomy for a previous clinically unilateral lesion. No lasting improvement has been observed following streptomycin in any of the patients in this category.

Group 5. Streptomycin has proved ineffective when given to patients suffering from advanced bilateral lesions, the treated patients and controls exhibiting no material difference in their progress, which is generally a downhill one. When the bilateral lesions are minor ones, conversion of the urines may occur.

The foregoing indicates the responses that have been obtained to the administration of 1 gm. of streptomycin daily for 90 days. The outstanding finding is an absence of any permanent beneficial effect in the presence of an established destructive renal lesion unless the focus can be extirpated by

surgery. It might be argued that a larger dosage, a more prolonged course, or both, would give better results than have been obtained in the Robroyston series. Lattimer *et al.* (1949) have, in fact, reported that the greatest percentage of conversions from positive urine to negative was obtained with patients who received the largest amount of the drug for the longest period. Thus 81 per cent. of their patients receiving 2 gm. of streptomycin daily for 120 days had an initial conversion of their urine from positive to negative, and 62 per cent. still had negative urines after 12 months. On the other hand, only 50 per cent. initial conversions resulted from treatment with 1 gm. daily for 42 days, and in six months the number remaining tubercle negative had fallen to zero. They state, however, that whilst lesions which cause no irregularity in a pyelogram probably respond well to chemotherapy, ulcerative lesions, as indicated in a pyelogram by clubbed or moth-eaten calyces, respond poorly for 'the layer of thick, necrotic, fibrous tissue surrounding them is so dense that the drug probably cannot penetrate it to reach the tubercle bacilli growing in the necrotic tissue.' A further statement that 'even a slight deformity of the pyelogram probably implies the presence of enough fibrous tissue to make the prognosis for medical treatment very poor' appears to explain the differences between the reported responses obtained in the American investigation and those at Robroyston. In the latter, patients with 'tubercle bacilluria' and no pyelographic abnormality are not included in the test at all. This category was deliberately excluded because minute subclinical lesions can heal spontaneously, with consequent disappearance of the tubercle bacilli from the urine. Because of this it was considered that it would be difficult to attribute any urine change to the streptomycin therapy. Lattimer confirms that 2 gm. for 120 days 'checked' only 25 per cent. of his cases 'who had a 'lesion large enough to be definitely visible in the pyelogram,' and that 'many of these cases became positive again after several months.'

Male Genital Tuberculosis

The streptomycin trial at Robroyston does not include genital tuberculosis but many of the male patients with renal tuberculosis have a coincidental genital involvement. The opportunity of observing the effects of the drug on this system is, therefore, frequently available and the responses are considered to be poor. Enlarged epididymes do not shrink, nodules do not disappear. In two instances the first signs of a genital involvement appeared when the patients were finishing their courses of treatment for the renal lesion. A similar lack of response has been noted in the

prostate and seminal vesicles, the induration and nodularities in these structures remaining. Superficial sinuses persisting after epididymectomy are, however, favourably influenced and heal quickly.

Para-aminosalicylic Acid (PAS)

PAS has been extensively used in the Scandinavian countries for the treatment of tuberculosis, following the discovery of its tuberculostatic effects by Lehmann of Gottenburgh in 1943. Clinical trials on pulmonary disease commenced in Sweden early in 1944, preceding by about half a year those with streptomycin in the United States. As the drug has only a slight solubility in acid it is scarcely absorbed from the stomach but is readily dissolved and absorbed in the intestine. Lehmann states that with the enteric coated granules the blood shows maximum values after about two hours, and after five to six hours a single dose of 4 gm. is excreted in high concentration in the urine. Patients sensitive to the drug may experience nausea, vomiting and diarrhoea, but it is not toxic to the liver, heart or kidney.

Ljunggren (1950) along with Obrant (1951) of Gottenburgh have used this form of chemotherapy for urinary tuberculosis during the past four years. Their present scheme is to combine the administration of PAS with conteben, one of the thiosemicarbazone drugs active against the tubercle bacillus. With the patients being cared for in a sanatorium, treatment is started with PAS, 8 to 14 gm. in divided doses of 2 gm., and conteben, 25 mg., each day. The conteben is gradually increased over a period of weeks to 100 mg. a day. Streptomycin, 1 gm. every second day, is added if the response to PAS and conteben is considered inadequate. Streptomycin is also routinely used on all patients who are to have surgical intervention. The chemotherapy is generally started at least two months before operation, and if a partial nephrectomy is contemplated the pre-operative therapy may be prolonged for six months, commencing with PAS and tebone, which can be administered over a long period without the risk of resistance. The streptomycin is added about a month before the operation.

On a recent visit to Sweden the writer had an opportunity of seeing the results of Ljunggren's methods at the Ravlanda Sanatorium near Gottenburgh. Patient's with established unilateral renal lesions continue as formerly to be treated by nephro-ureterectomy, nephrectomy or partial nephrectomy, for it is reckoned that chemotherapeutic agents cannot reach such foci. It is considered, however, that the treatment diminishes the risk of the disease becoming generalized after operation, with a consequent decrease in early

post-operative mortality. An improvement in wound healing has been observed, enabling partial nephrectomy or any other renal operation to be undertaken without fear of the wound breaking down. The symptoms caused by secondary cystitis quickly improve, and superficial bladder ulceration clears without the aid of local treatment. Many conversions of tubercle positive urines to negative have been obtained in the bacilluria of a variety of the disease, and also in some with minute though pyelographically discernible lesions. Figures are not yet available showing the incidence or duration of these conversions. Stress is laid on continuing treatment until three or four consecutive negative guinea-pig tests have been obtained at intervals of four to six weeks.

The experiences of the Swedish trials suggest that PAS, possibly in conjunction with the thiosemicarbazones, should be employed as an adjunct to streptomycin for urinary tuberculosis. Cosbie, Ross *et al.* (1951) have not been impressed with the enhancement of the therapeutic effects which follow the use of PAS in combination with streptomycin, and they too are now testing the results of treatment with a combination of the three preparations.

Conclusions

Histological examinations of kidneys and of resected segments removed after chemotherapy have sometimes revealed evidence indicating a tendency to healing, and a few isolated reports of complete healing have been made. There are, however, no known chemotherapeutic agents, alone or in combination, which can be depended on to cure or control an established renal focus. The rôle of chemotherapy is therefore as an adjunct to other forms of treatment. Prolonged sanatorium care, and, when possible nephrectomy, or excision of the kidney focus, remain the optimum methods of dealing with renal tuberculosis. From chemotherapy the following benefits may be expected:

(a) A tubercle positive urine can be rendered tubercle negative. In the presence of a renal focus of more than microscopic dimensions, this change, however, is likely to be a transitory one.

(b) Mild secondary cystitis and superficial bladder ulceration generally responds to the treatment with a corresponding improvement in symptoms. These benefits are chiefly observed in the group suffering from clinical unilateral renal lesions on whom nephrectomy has been performed.

(c) As an 'umbrella' for nephrectomy, partial nephrectomy or epididymectomy, streptomycin is probably a safeguard in preventing haematogenous dissemination and sinus formation.

It should be remembered that because of the

increased tendency to cicatrization associated with streptomycin therapy, sequelae of a character that worsens the condition of the patient may result. It is not, therefore, permissible to give the treatment indiscriminately with the idea that should no benefit be obtained no harm will have followed the attempt. The drug should be withheld in the following circumstances:—

(a) Urinary tuberculosis associated with advanced bilateral renal lesions or an advanced lesion in a solitary kidney; no benefit can be expected from the treatment and the risk of toxic symptoms is not, therefore, worth taking.

(b) A severe constriction at the ureterovesical junction or a well-marked ureteric stricture particularly when associated with a single kidney; the increased cicatrization resulting from the streptomycin may be followed by hydronephrosis and hydroureter necessitating uretero-intestinal anastomosis or ureterostomy to save the kidney from a progressive destruction due to back pressure.

(c) Severe secondary cystitis associated with marked bladder contracture; advanced bladder involvement of this type is rarely improved and the contracture may be worsened as a result of the increasing cicatrization.

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