In our pregnancy cardiac clinic at the Manchester Royal Infirmary the almoner plays an important part. Her experience enables her to resolve many of the patients' difficulties and to arrange home help, to tide over the emergency, in case of need. From the psychological aspect, also, we believe this special clinic has proved useful. The newcomers get talking with the old hands, who have been through the mill before, and begin to realize that heart disease is not nearly such a terrible thing as they had been led to believe.

James Mackenzie

I cannot conclude my lecture without reference to the work of a very remarkable man—a man who was keenly interested in this problem and who wrote a book on heart disease in pregnancy (Mackenzie, 1921). He must have been a familiar figure to the older members of my audience, for he spent the Indian summer of his life in St. Andrews.

James Mackenzie was a Highlander. He was educated at Perth Academy and Edinburgh University. The next twenty-five years—the most productive years of his life—were devoted to general practice in Burnley. His work there is commemorated by a tablet on the wall of the house in which he practised. During the war this tablet was removed, for the powers that be considered that the word "Burnley," which appeared in the inscription, might prove helpful to the enemy in the event of invasion.

As an undergraduate Mackenzie won no special academic distinction. Later, however, he proved himself to be an investigator of outstanding merit and a man who made the fullest possible use of his opportunities. Mackenzie will probably go down to history as the man who solved the riddle of the cardiac irregularities. This he did by means of his clinical polygraph; all the earlier models of this instrument were made for him by Mr. Shaw, a local watchmaker.

But far more important was his work on prognosis, based on his own clinical observations. I have never ceased to marvel that such a popular and busy family doctor could find the time, and have the energy, to keep such wonderful records of his cases. The hours for research were literally snatched from the rush of general practice. It was these records of his cases in Burnley which enabled Mackenzie finally to overthrow the dictatorship of the stethoscope, which had dominated cardiology for nearly a hundred years.

Summary

The chief dangers to be faced in patients with heart disease who are pregnant are acute pulmonary oedema and congestive heart failure. The former calls for special vigilance on account of the suddenness with which it may develop, and in every case of mitral stenosis clinical or radiological evidence of pulmonary congestion must be regarded with grave apprehension. Congestive heart failure with oedema, if recognized early, usually responds well to treatment.

Auricular fibrillation, though a recognized precursor of heart failure, is not necessarily a bar to pregnancy, provided adequate antenatal and post-natal care can be assured. In assessing the risk, the previous obstetric history, age, economic conditions, and temperament of the patient must all be taken into account.

In patients with heart failure, surgical intervention should never be contemplated until the heart failure has been treated. Patients with heart disease tolerate pelvic delivery better than caesarean section.

In patients with advanced heart disease pregnancy is contraindicated. If, however, pregnancy is already established and the patient is seen within the first three months, it should be terminated, but, if she is not seen until later, it should be allowed to run its normal course. Alternatively, mitral valvotomy may be considered.

There is no purely cardiac indication for anticipating normal delivery.

All patients, however trivial their heart disease, should be kept under observation throughout pregnancy, and intercurrent infection and anaemia promptly treated.

REFERENCES

- Baker, C., Brock, R. C., Campbell, M., and Wood, P. (1952). *British Medical Journal*, 1, 1043.
 Bramwell, C. (1948). *Lancet*, 2, 481.
 — and Jones, A. M. (1944). *Brit. Heart J.*, 6, 129.
 — and Longson, E. A. (1938). *Heart Disease in Pregnancy*. London.
 Carr, F. B., and Hamilton, B. E. (1933). *Amer. J. Obstet. Gynec.*, 26, 824.
 Gilchrist, A. R., and Murray-Lyon, R. M. (1933). *Edinb. med. J.*, 40, 587.
 Haigh, D. C., and Gilchrist, A. R. (1949). *Trans. Edinb. Obstet. Soc.*, p. 55.
 Hunt, G. H. (1926). *Guy's Hosp. Rep.*, 76, 135.
 Jones, A. M. (1952). *Practitioner*, 169, 49.
 Logan, A., and Turner, R. (1952). *Lancet*, 1, 1286.
 Mackenzie, J. (1921). *Heart Disease and Pregnancy*. London.
 Robinson, A. L. (1927). *Lancet*, 1, 170.
 Watson, B. P. (1933). *Amer. J. Obstet. Gynec.*, 26, 838.

TREATMENT OF GENITO-URINARY TUBERCULOSIS FURTHER REPORT

BY

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In 1951 we published a preliminary report on the treatment of 51 cases of genito-urinary tuberculosis (Ross *et al.*, 1951). The present communication includes a record of a further 47 patients similarly treated, and a follow-up of the earlier series. It is necessary to emphasize once more that a long-term view must be taken of this disease, as it is possible to encounter patients who have survived for many years after a bilateral renal lesion has been confirmed and in spite of the absence of treatment of any kind.

Classification.—No patient was accepted for treatment until a positive guinea-pig inoculation test put the diagnosis beyond all reasonable doubt. At the same time no case, however serious, was refused treatment. The patients were divided in five groups: (1) minor unilateral lesion or subclinical focus; (2) lesion of one kidney with cystitis and nephrectomy; (3) bilateral disease and nephrectomy of the worse kidney; (4) infection of the remaining kidney; and (5) severe bilateral disease. We realize that this is not a perfect classification, but for the purpose of uniformity in assessing the results we have not altered it on this occasion.

Method of Treatment

In addition to the regime described below, the ordinary surgical measures, such as nephrectomy and epididymectomy, were carried out when required, with the proviso that the optimum time was selected for the operation. For example, nephrectomy was often performed during the second or third course of streptomycin.

The whole course of treatment lasted six months, during which time the patient received the usual sanatorium regime at Wrightington Hospital. The three drugs used were: (a) "Ethizone" (*para*-ethylsulphonylbenzaldehyde thiosemicarbazone, or T.B.3), beginning at 50 mg. daily and gradually increasing by weekly increments of 200 mg. daily. Ethizone was given continuously for the six-months course of treat-

ment. (b) *Para-aminosalicylic acid* (P.A.S.), 18 g. daily, given at three-hourly intervals for periods of 25 days, alternating with (c) dihydrostreptomycin, 1 g. twice a day for a period of 35 days. A mixture containing 30 gr. (2 g.) of potassium citrate and 5 gr. (0.32 g.) of potassium iodide was given thrice daily throughout the streptomycin periods.

Originally it was a difficult matter to render and maintain the urine alkaline, but as a result of recent extended tests we have found the following mixture both palatable and effective:

Potassium citrate	..	..	..	30 gr. (2 g.)
Sodium citrate	..	..	..	30 gr. (2 g.)
Potassium acetate	..	..	..	20 gr. (1.3 g.)
Syrup of lemon	..	..	..	7½ min. (0.45 ml.)
Extract of liquorice	..	..	..	7 min. (0.42 ml.)
Aqua	..	..	..	ad ½ oz. (14 ml.)
½ oz. (14 ml.) four times a day				

We have already given our reasons for this method of treatment (Ross *et al.*, 1951), which has been gradually evolved as a result of experience. Briefly these reasons are:

(1) Each of the three drugs probably exerts a different effect on the tubercle bacillus, and it seems logical to use all three in the hope of achieving the maximum effect.

(2) Lattimer *et al.* (1950) have shown that in order to maintain an adequate concentration of streptomycin in the blood it is desirable to give 1 g. every twelve hours. The concentration in the blood following intramuscular injection of 1 g. of streptomycin is as follows:

1 hour	..	..	14-31 u./ml.	6 hours	..	..	8-15 u./ml.
2 hours	..	..	22-38 "	7 "	..	..	6-10 "
3 "	..	..	18-22 "	10 "	..	..	5-9 "
4 "	..	..	14-18 "	12 "	..	..	3-4-5 "
5 "	..	..	10-13 "				

(3) Lattimer *et al.* also pointed out that the incidence of toxicity rapidly increased after 60 days and was invariably present at 120 days, using 2 g. of streptomycin daily. We have therefore adopted the intermittent method of administering streptomycin to counteract this tendency.

(4) By using the alternating technique we hoped not only to prevent the emergence of resistant strains of tubercle bacilli, but also to diminish the intolerance of patients to the larger doses of P.A.S.

(5) Ethizone was given continuously, as it has been shown by Domagk *et al.* (1946) that the best results were obtained after prolonged administration. Ethizone seems to be the most active and least toxic of the thiosemicarbazones (Hoggarth *et al.*, 1949; Hoggarth and Martin, 1950). There is evidence to show by the "corneal screening" test that the effects of both P.A.S. and streptomycin are enhanced by ethizone (Rees and Robson, 1950, 1951).

Surgical Measures

During the course of treatment nephrectomy was performed on 13 patients, the ureter being excised only as far as the pelvic brim. The wound was invariably closed without drainage, and in every case healed by first intention. With the introduction of antibiotics it would seem that partial or polar nephrectomy may prove of value. Partial nephrectomy has not been carried out in the present series, but has been performed on several occasions in the third group of cases, to be published at a later date.

Epididymectomy was found to be necessary in 12 patients, and was carried out by the Ross (1948) technique. Healing was satisfactory, and in no instance did atrophy of the testicular body occur.

Three patients required transplantation of the ureter of the remaining kidney into the colon. All three were advanced cases (type 4), and two patients died some months after the operation. The third patient has remained well. We believe that the two deaths were due to acidosis and uraemia, and hope to eliminate these tragedies in future by maintaining a close watch on the blood chemistry for a prolonged period. As routine measures we insist on a low-salt diet, a strong alkaline mixture, and three-hourly evacuation of the bowels day and night.

Toxicity

In view of the fact that potent drugs were being used over an extended period of six months it seemed important that signs of toxicity should be recognized and dealt with at the earliest possible moment.

P.A.S.—This has been extensively employed in the treatment of all forms of tuberculosis, and many workers experienced in its use have testified to its low toxicity (Nagley, 1949; McAnally and Seymour, 1948). In spite of this we have found some minor toxic symptoms in 35% of our patients, especially nausea, vomiting, anorexia, and mental depression. In a further 25% the drug had to be discontinued because of severe vomiting, despite the fact that all varieties and forms, such as the calcium salt, cachets, and enteric-coated granules, were given a trial. We have not encountered haematuria or albuminuria (Nagley and Logg, 1949), nor have we seen any skin eruptions. Two patients developed toxic hepatitis (Gow, 1951) similar to those previously reported (Cuthbert, 1950; McKendrick, 1951). There was no clinical evidence of potassium depletion (Heard *et al.*, 1950; Cayley, 1950) in this series. Thus it can be seen that until a less toxic form of P.A.S. is available the full value of the drug cannot be achieved in an appreciable number of patients. For this reason we are now using the calcium salt of B.P.A.S. (N-benzoyl *para*-aminosalicylic acid) (Gow, 1953).

Dihydrostreptomycin.—In spite of using the intermittent method of administration outlined above, we have encountered an appreciable number of toxic manifestations. In the present series of 47 patients deafness has occurred in six, dizziness in eight, and both symptoms in two. Skin rashes were found in three cases. The dizziness and skin rashes were transient and disappeared quickly when the drug was stopped. Desensitization was often effective, and was carried out by beginning with a daily injection of 0.1 g. of streptomycin, gradually increasing up to 1 g., the course lasting a fortnight. The administration of "avomine," one of the antihistaminic drugs, was also helpful. Deafness was a more serious symptom, and appears to be permanent. These figures correspond with those quoted from a smaller series (Cathie and Garrow, 1951; Don and Gregory, 1952; etc.). It would seem that the percentage of patients becoming deaf with dihydrostreptomycin is much higher than with streptomycin sulphate, although the activity of the two preparations is the same. In future, therefore, we intend to use the latter.

Ethizone.—We have not seen any of the more severe complications described, such as liver or renal damage, but as a precautionary measure we have carried out at regular intervals the thymol turbidity test on patients' sera. All findings were below 4 units, which, at the very least, indicates that there has been no gross liver damage. In a few instances, in which toxæmia from the disease was severe, there has been a progressive anaemia, which improved, irrespective of the ethizone, when the tuberculous focus producing the toxæmia was removed. In no case was the ethizone stopped. All patients were able to tolerate 150 mg. daily, but 30% were not able to take 200 mg. for prolonged periods. Intolerance of the higher dose was manifested by anorexia, depression, and mental apathy. Patients under treatment with thiosemicarbazone, and ethizone in particular, should abstain from alcohol on account of its reaction. The symptoms of this are palpitation, flushing of the skin, and a full bounding pulse. If the effect is severe, collapse may occur. These symptoms may last two to three hours. They can also be experienced in a minor degree for about seven to ten days after the ethizone has been discontinued.

Results

As in our previous communication, we have attempted to assess the results in the following way: (a) sterilization of the urine; (b) radiographic changes; (c) cystoscopic improvement, including an increase in bladder capacity and

an improvement in the appearance of the mucous membrane or ureters; and (d) clinical improvement—for example, frequency of micturition, dysuria, gain in weight.

(a) Sterilization of the Urine

We have always believed that the sterilization of the urine is the absolute criterion of the efficacy of any particular method of treatment. We have therefore taken special care to ensure that the technique employed should eliminate as many sources of error as possible.

During the period of treatment the urines were investigated for the presence of tubercle bacilli at approximately six-weekly intervals. Every effort was made to isolate the bacillus, and the methods used for this were modified from time to time in order to improve the results.

In the early stages of the investigation the six-weekly search for tubercle bacilli was carried out on the total quantity of urine passed by the patient over a period of 40 hours. The collection of this urine was carried out as follows: (a) A 24-hour pooled specimen. (b) The "first morning" specimen passed by the patient after the end of the 24-hour period. (c) A catheter specimen obtained from the patient four to five hours after the first morning specimen had been passed.

The 24-hour specimens were allowed to stand for 48 hours, and 150 ml. of the deposit was removed and centrifuged. The centrifuged deposit was treated for a minimum time with 3% sodium hydroxide to destroy contaminating organisms. After neutralization it was inoculated on two Löwenstein-Jensen slopes and, except in some of the earlier cases, into two guinea-pigs.

From the first morning specimen 100 ml. was centrifuged and the deposit, after treatment with 3% sodium hydroxide, was inoculated on two Löwenstein-Jensen slopes.

The catheter specimens were used in an effort to overcome the possibility that the sodium hydroxide needed to destroy contaminating organisms might reduce the number of positive results by its lethal action on the tubercle bacilli. Each specimen was collected with the utmost aseptic precautions, using a no-touch technique. The whole specimen was centrifuged and a small part of the deposit inoculated on to a blood-agar plate. If no growth appeared on overnight culture the specimen was regarded as free of contaminants and inoculated without further treatment on two Löwenstein-Jensen slopes. If contaminating organisms grew on the blood-agar plate the deposit was treated with sodium hydroxide before inoculation.

Thus each investigation entailed the inoculation of six Löwenstein-Jensen slopes and two guinea-pigs. The results obtained from these specimens are given in Table I. These

TABLE I

Type of Specimen	No. of Specimens	Positive	
		No.	% (Approx.)
24-hour: culture	99	8	8
" guinea-pig	48	13	27
First morning: culture ..	97	7	7
Catheter, no contaminants (no sodium hydroxide used) ..	39	1	2.5
Catheter, contaminated (treated with sodium hydroxide) ..	47	1	2

results revealed a number of facts: (a) That early morning specimens were giving results equally as good as those obtained from the 24-hour specimens. (b) That, in spite of the greatest possible care, more than half the catheter specimens were bacteriologically contaminated. (c) That the results of culture of catheter specimens compared unfavourably with those obtained from early morning and 24-hour specimens. This applied whether the catheter specimens were treated or untreated with sodium hydroxide. (d) That guinea-pig inoculation of the deposits was giving better results than cultural methods.

For these reasons both the methods of collecting specimens and their examination were changed. The specimens were limited to 24-hour pooled urines and first morning specimens.

The 24-hour specimens were allowed to stand for 48 hours. At the end of this period the whole of the thick deposit ("sludge") was withdrawn. An equal volume of the urine lying immediately above it (supernatant) was also withdrawn into a separate container. These two specimens, each about 50–100 ml. in volume, were centrifuged, and the deposits treated with sodium hydroxide and neutralized. The resultant mixtures were divided into two. One-half of each was inoculated on two Löwenstein-Jensen slopes. The other half of one of them was inoculated into two guinea-pigs.

The first morning urine was treated in the same manner as in the early cases, except that the deposit was inoculated on two Löwenstein-Jensen slopes and also into two guinea-pigs. By this means, on each six-weekly investigation the deposits from 36 hours' urine were inoculated on six Löwenstein-Jensen slopes and into four guinea-pigs. The results are given in Table II.

TABLE II

Specimen	No.	Positive	
		No.	% (Approx.)
Early morning: culture	102	6	6
" guinea-pig	102	18	18
24-hour "sludge": culture ..	108	5	4.5
" guinea-pig	62	7	11
"Supernatant": culture	99	7	7
" guinea-pig	47	4	8.5

Examination of results at this stage led us to draw certain inferences: (a) That once again the results from the early morning specimens were at least as good as those from the 24-hour pooled specimens. (b) That guinea-pig inoculation was still giving better results than cultural methods. (c) That the distribution of tubercle bacilli in the "sludge" and the urine layer immediately above it was more or less uniform. (d) That the use of smaller volumes of deposit from the 24-hour specimens was apparently leading to somewhat poorer results.

A further change was therefore made in the technique. The 24-hour specimens were allowed to stand for 48 hours and a minimum of 200–300 ml. was centrifuged, the resultant deposit being treated with sodium hydroxide and inoculated on two Löwenstein-Jensen slopes and into two guinea-pigs. The whole of the early morning specimens were centrifuged and the deposit was inoculated on two Löwenstein-Jensen slopes and into two guinea-pigs. The results obtained by this method are given in Table III.

By this means we obtained the greatest proportion of positive results both in the early morning specimens and in the 24-hour specimens. Once again guinea-pig inoculation

TABLE III

Specimen	No.	Positive	
		No.	%
Early morning: culture	93	12	13
" guinea-pig	93	26	28
24-hour: culture	135	13	8
" guinea-pig	135	42	31

TABLE IV

Specimen	No.	Positive	
		No.	%
Early morning: culture	292	26	8.9
" guinea-pig	193	46	24
24-hour: culture	441	22	5
" guinea-pig	284	68	24

gave better results than artificial culture, and the results from the early morning specimens were at least as good as those from the 24-hour specimens.

The total figures for the whole period are given in Table IV.

Table V reveals that out of the total of 47 patients investigated the urines of 36 (76.5%) were sterile at the end of the six-months course of treatment. Of the 11 (23.5%) who were

(b) Radiographic Changes

In no case was there any convincing improvement in the pyelographic appearances during treatment (Table VI). Intravenous pyelography has been carried out in every patient and a bilateral retrograde pyelogram whenever possible. We do not agree with Ericsson and Lindbom (1950) that retrograde pyelography is dangerous, and we have seen no complications in many hundreds of such examinations.

TABLE V.—Sterilization of Urine and Sensitivity of Organisms to Streptomycin

Group	Initially Guinea-pig Positive	After 2-3 Months' Treatment			After 3-4 Months' Treatment			After 5-6 Months' Treatment			Remarks
		Guinea-pig Positive		Sensitive to Streptomycin	Guinea-pig Positive		Sensitive to Streptomycin	Guinea-pig Positive		Sensitive to Streptomycin	
1	16	No. 4	% 25	All sensitive to 0.25 u./ml.,	No. 6	% 37	5 sensitive to 0.25 u./ml., 1 resistant to 32 u./ml.	No. 5	% 32	4 sensitive to 0.25 u./ml. 1 resistant to 64 u./ml.	Of 4 patients who were guinea-pig positive after 2 months, 3 remained positive and 1 became negative. After 4 months' treatment, 3 patients who were guinea-pig negative reverted after 4 months' treatment. Two of these remained positive after 6 months No new guinea-pig positives were noted during the course of treatment One patient who was guinea-pig positive at the fourth month became negative at the sixth month of treatment and 1 who was guinea-pig negative reverted to positive at the end of the sixth month The 2 patients who were positive at 4 months had transplantation of the ureter into the colon The patient who was positive died during the fourth month of treatment with silicosis and acute bronchopneumonic spread
2	8	5	62	„ „	5	62	4 sensitive to 0.25 u./ml., 1 resistant to 64 u./ml.	3	37	2 sensitive to 0.25 u./ml., 1 resistant to 64 u./ml.	
3	10	5	50	4 sensitive to 0.25 u./ml., 1 resistant to 32 u./ml.	3	30	1 sensitive to 0.25 u./ml., 2 resistant to 32 u./ml.	3	30	1 sensitive to 0.25 u./ml., 2 resistant to 32 u./ml.	
4	9	5	55	All sensitive to 0.25 u./ml.	2	22	Both sensitive to 0.25 u./ml.	—	—	—	
5	4	1	20	Sensitive to 0.25 u./ml.	—	—	—	—	—	—	
Total	47	20	42	19 sensitive to 0.25 u./ml., 1 resistant to 32 u./ml.	16	34	12 sensitive to 0.25 u./ml., 4 resistant to 32 u./ml.	11	23	7 sensitive to 0.25 u./ml., 4 resistant to 32 u./ml.	

positive four were resistant to streptomycin, two of whom had had over 150 g. of streptomycin elsewhere, before beginning our course of treatment. Occasionally tubercle bacilli have reappeared (after previous negative guinea-pig tests) in the urine of a patient during the latter half of the course of treatment. It is probable that the excretion of tubercle bacilli is intermittent except when the lesion is large and has a free communication with a calix. Again, the kidney may be reinfected from an active focus elsewhere, such as the spine or lung. It must be remembered that sometimes a secondary infection with other organisms, usually *Bact. coli*, may complicate matters and require treatment by the appropriate antibiotic. It is unfortunate that, owing to the somewhat indiscriminate and widespread use of antibiotics without bacteriological control, so many resistant strains of organisms were encountered.

It is desirable to carry out the retrograde pyelogram under direct vision in order to obtain an accurate picture of the pelvi-caliceal system. Recent experience with partial or polar nephrectomy has, however, made it clear to us that relatively extensive lesions may lie alongside a calix showing minimal deformity.

(c) Cystoscopic Improvement

In the course of this investigation over 200 cystoscopies and 150 ureteric catheterizations were carried out in the period January 1 to December 21, 1951. All cystoscopic examinations were done by two of us (J. C. R. and J. G. G.), and in each case a careful description of the bladder mucosa and the ureteric orifices was written without reference to previous cystoscopic notes. Definite improvement was found in all cases in the present series (in which the bladder

TABLE VI

Group	No. of Cases	Clinical Improvement									Cystoscopic Changes								Pyelographic Changes			
		Frequency of Micturition				Pain on Micturition				Weight	Bladder Appearance				Bladder Capacity							
		Normal	Unchanged	Improved	Deteriorated	Normal	Unchanged	Improved	Deteriorated		Normal	Unchanged	Improved	Deteriorated	Normal	Unchanged	Improved	Deteriorated	Normal	Unchanged	Improved	Deteriorated
1	16	10	—	6	—	14	—	2	—	11 gained, average 10 lb.; 5 lost, average 3 lb.	10	—	6	—	14	—	2	—	10	5	—	1
2	7	—	1	6	—	6	—	1	—	7 gained, average 14 lb.	—	—	7	—	4	—	3	—	—	6	—	1
3	10	—	2	8	—	2	2	6	—	6 gained, average 8 lb.; 4 lost, average 2 lb.	—	2	8	—	—	1	9	—	—	10	—	—
4	10	—	6	3	1	—	10	—	—	7 gained, average 6 lb.; 3 lost, average 4 lb.	—	3	4	3	5	3	—	2	—	7	—	—
5	4	—	—	4	—	—	1	3	—	2 gained 12 lb.; 2 lost, 1 4 lb., 1 6 lb.	—	1	3	—	—	1	2	—	—	4	—	—

was diseased) except for three (Table VI). The improvement consisted in the healing of granulations and ulceration and replacement of these by scar tissue, in addition to an increase in bladder capacity.

(d) Clinical Improvement

We have noticed that clinical improvement usually occurs at an early stage of the course, but in some patients it appears later, sometimes after three months' treatment. In almost every patient a clinical improvement was achieved and was assessed in terms of degree of frequency, nocturia, dysuria, etc. It is customary to denigrate in scientific communications all references to symptoms, but the symptomatic

TABLE VII.—Effect of the Regime on the Extrarenal Lesion

Chest lesions	12	<div>Improved 3</div> <div>Deteriorated 1</div> <div>Unchanged 8</div>	4 quiescent before treatment began
Bone and joint lesions	3	<div>Unchanged 2</div> <div>Deteriorated 1</div>	2 quiescent before treatment began
Bone and joint and chest lesions	3	<div>Improved 1</div> <div>Unchanged 2</div>	1 quiescent before treatment began
	3	<div>Improved 1</div> <div>Unchanged 2</div>	2 quiescent before treatment began

improvement is vitally important from two points of view. The improvement is important to the patient not only because he is able to obtain more comfort and sleep, but also because he is encouraged to continue and complete his six-months course. The results are shown in Table VI.

Table VII shows the results in patients having combined lesions affecting also lungs, bones, joints, etc. In combined cases there is no significant improvement of the extrarenal lesion when compared with cases treated with streptomycin alone, or, as in the case of the lungs, with streptomycin and P.A.S. One important fact which should be mentioned, however, is that the seven patients whose sputa remained positive for tubercle bacilli at the end of the six-months period were all sensitive to 0.25 u./ml. of streptomycin.

Follow-up of Previous Series (Table VIII)

The group of 51 patients discussed in a previous article (Ross *et al.*, 1951) have been followed up on the lines indicated above. With few exceptions symptomatic and cystoscopic improvement has been maintained up to the present time, eighteen months since the completion of treatment. Of the remaining 43 patients of the original series still alive, the urine of 27 was sterile at 18 months.

The follow-up included a three-monthly cystoscopy and an inoculation of guinea-pigs with the deposit of both 24-hour and ureteric specimens of urine. It must be pointed out that the six patients given all three drugs were advanced cases falling into either type 4 or type 5. On the whole, the alternating method of treatment described here seems to be standing up to the test of time.

Two patients appeared to merit special mention, as they illustrated the fact that no case should be regarded as hopeless. The first man was admitted with active pulmonary and vertebral lesions, a tuberculous kidney, cystitis, and epididymitis. During his six months' treatment his extra-renal lesions healed and we were able to remove the non-functioning right kidney. Incidentally, this was the only patient in the series in whom complete healing of the epididymal lesion took place without operation.

In a second patient with a disorganized kidney operation revealed the presence also of a large solitary cyst. This is only the third case of tuberculous nephritis in which a solitary cyst has been recorded. It is interesting that the amount of streptomycin in the cyst was 250 u./ml. fluid, whilst the greatest amount in any ulcero-cavernous lesion was 8 u./ml.

Summary

An investigation begun two years ago has been carried a step forward by treating a further 47 patients.

The six-months course consists in a sanatorium regime, the usual surgical measures, and a combination of streptomycin, P.A.S., and ethizone. Our view still remains that the three drugs are not a substitute for surgery or sanatorium treatment, but that each is a complement to the other.

Assessment of the results has been carried out not only for the present series of patients but also for the original group of 51 reported a year ago. The most important single factor is the elimination of tubercle bacilli from the urine. To be certain of this, most exhaustive and searching tests were found to be necessary. Of the original group 62% of urines were sterile at the end of eighteen months, while 77% of urines of the present series were sterile at the end of a year.

While it is necessary to keep in mind the chronicity of the disease, the course of treatment suggested by us seems to achieve satisfactory results and to hold out a promise for the future.

We are grateful to Mr. J. Dobson, surgeon-superintendent, Wrightington Hospital, for his assistance and constant encouragement, to Herts Pharmaceuticals Ltd. for their interest,

TABLE VIII

Treatment	No. of Cases	6 Months	12 Months	18 Months
Streptomycin alone	18	<div>13 remained sterile</div> <div>3 positive</div> <div>2 sterile, reverted to positive</div>	<div>9 sterile</div> <div>3 reverted</div> <div>1 given other course</div> <div>3 died after transplantation of ureter</div> <div>2 sterile</div>	<div>9 sterile</div> <div>2 reverted</div> <div>1 not traced</div> <div>2 sterile</div> <div>4 sterile</div>
Streptomycin and P.A.S. together	7	<div>4 sterile</div> <div>1 positive</div> <div>2 sterile, reverted to positive</div>	<div>4 sterile</div> <div>Died after ureterocolic transplant</div> <div>1 died after ureterocolic transplant</div> <div>1 given latest course</div>	
Streptomycin and P.A.S. alternately	20	<div>19 sterile</div> <div>1 positive</div>	<div>1 not traced</div> <div>2 given latest course</div> <div>12 sterile</div> <div>1 died after thoracoplasty</div> <div>Died after ureterocolic transplant</div>	<div>10 sterile, 2 reverted, 1 died</div> <div>2 still positive</div>
Streptomycin, P.A.S., and thiazetazone (T.B.1)	6	<div>1 positive</div> <div>6 sterile</div>	<div>4 sterile</div> <div>2 reverted</div>	<div>2 sterile, 2 reverted</div> <div>2 still positive</div>
Total	51	Sterile 42 (82%)	<div>1 not traced; 7 died after ureterocolic transplant; 4 given latest course</div> <div>No. followed up, 39</div> <div>Sterile 29 (74%)</div>	<div>1 not traced</div> <div>1 died</div> <div>Total followed up, 37</div> <div>Sterile 23 (62%)</div>

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REFERENCES

- Cathie, I. A. B., and Garrow, D. H. (1951). *British Medical Journal*, 2, 735.
 Cayley, F. E. de W. (1950). *Lancet*, 1, 447.
 Cuthbert, J. (1950). *Ibid.*, 2, 209.
 Domagk, G., Behnisch, R., Mietzsch, F., and Schmidt, H. (1946). *Naturwissenschaften*, 33, 315.
 Don, C., and Gregory, J. (1952). *Lancet*, 1, 72.
 Ericsson, N. O., and Lindbom, A. (1950). *Brit. J. Urol.*, 22, 201.
 Gow, J. G. (1951). *Lancet*, 2, 941.
 — (1953). *British Medical Journal*, 1, 95.
 Heard, K. H., Campbell, A. H., and Hurley, J. J. (1950). *Med. J. Aust.*, 2, 606.
 Hoggarth, E., and Martin, A. R. (1950). *Brit. J. Pharmacol.*, 5, 188.
 — Young, E. H. P., and Storey, N. E. (1949). *Ibid.*, 4, 248.
 Lattimer, J. K., Amberson, J. B., and Braham, S. (1950). *Amer. Rev. Tuberc.*, 61, 518.
 McAnally, D., and Seymour, D. E. (1948). *Lancet*, 1, 303.
 McKendrick, G. D. W. (1951). *Ibid.*, 2, 668.
 Nagley, M. M. (1949). *Practitioner*, 163, 459.
 — and Logg, M. H. (1949). *Lancet*, 1, 913.
 Rees, R. J. W., and Robson, J. M. (1950). *Brit. J. Pharmacol.*, 5, 77.
 — (1951). *Ibid.*, 6, 83.
 Ross, J. C. (1948). *Brit. J. Urol.*, 20, 173.
 — Gow, J. G., and St. Hill, C. A. (1951). *Lancet*, 1, 1033.

THE SIGNIFICANCE OF THE THYROID IN PSYCHIATRIC ILLNESS AND TREATMENT

ROUTINE EXAMINATION WITH A RADIOACTIVE TRACER METHOD

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In previous communications we reported that abnormal indices of thyroid activity occur in a fair proportion of psychiatric patients (Reiss *et al.*, 1951b). Changes in the thyroid activity of such patients after E.C.T. and treatment with pituitary anterior lobe hormones were described (Reiss *et al.*, 1951a).

The thyroid activity is now investigated as a routine in the majority of patients admitted to our hospital, so that we have extended the studies further, and here report on some of the results of this work in more than 1,000 patients in 1949–50 and 1950–1. The question of whether there is a real causal interrelationship between ascertained thyroid disturbance and mental illness is examined in the light of these research results.

Methods.—The radioactive tracer methods used have already been described (Haigh and Reiss, 1950; Reiss *et al.*, 1952). The normal ranges are seen in Fig. 3. For the determination of the basal metabolism rate the usual spirometric method was used. Where complete relaxation of the patient could not be obtained the investigation was carried out under thiopentone. Methods of treatment are referred to in the description of each case.

Results

Distribution of Thyroid Indices

Figs. 1 and 2 are histograms of the distribution of the I₁ values in 302 male and 244 female psychiatric patients in 1949–50, and of 222 male and 271 female similar cases in 1950–1. Fig. 3 shows the histograms of the patients in

1949–50 superimposed on the histograms of 1950–1. The distribution of thyroid indices in about 1,000 unselected psychiatric patients in two successive years is seen to be almost exactly the same. For comparison, the limits for normal controls are plotted above the histograms of Fig. 3, and the arithmetic mean values are in good agreement for the corresponding values of the normal controls. These normal control values never overlapped the values recorded in patients who had clinical evidence of hypothyrosis or hyperthyrosis. It is clear that the spread of the patient material is much wider than the spread of the normals, and that among the patients there are a number in whom thyroid function lies outside the normal range but in whom clinical evidence of thyroid abnormality is lacking. The number of these borderline cases is appreciable, amounting to about 20%. The mean values of the thyroid indices in males are lower than in females, both in patients and in normal controls. In male borderline cases thyroid function tends towards hypothyroidism, and in females to hyperthyroidism.

Distribution of Thyroid Indices According to Certain Psychiatric Disease Categories

The cases were classified in a number of fairly well defined psychiatric categories, and the relation between these psychiatric disorders and their associated thyroid values is shown in Fig. 4. For this purpose the thyroid values were classified in four standards, as follows: the normal range was divided equally into upper and lower normal; outside these limits are the regions of underfunction and overfunction, which comprise mainly borderline cases.

In most groups there seems to be no significant relationship between the disease and the standard of thyroid function. There are, however, the following exceptions. In the female anxiety group there is a tendency to thyroid hyperfunction, more than 60% of the cases being in the upper normal or overfunctional range. In contrast, in the male anxiety group there is a tendency to thyroid underfunction, about 36% being lower normal and 38% underfunctional.

In 40% of female patients with recent schizophrenia the thyroid index was above the upper range of normality, but in female chronic schizophrenia this was seldom observed. In male recent schizophrenia, by contrast, underfunction of the thyroid was more usual.

Changes in Thyroid Function Accompanying Changes in the Psychiatric Illness Occurring Spontaneously or after Treatment

We have previously reported (Reiss *et al.*, 1951a) the effect of E.C.T. on thyroid function. The cases investigated were mainly depressives, which usually recover with E.C.T., and the series was small (34 cases). We have extended the investigation to include a more representative group of 183 cases of most common forms of psychiatric disorder treated in various ways or remitting spontaneously. Thyroid function was assessed before and after treatment, and compared with the clinical result. The forms of treatment included E.C.T., modified insulin, coma insulin, carbon dioxide, leucotomy, psychotherapy, and various combinations. A number of cases in which there was a spontaneous remission were also investigated.

In 76 of these patients there was evidence of disturbed thyroid function before treatment, and normal values in 107. Changes in the thyroid values of all the patients after treatment are shown in Tables I–III. In 82 of the 107 euthyroid cases (Table I) treatment produced no change or

TABLE I.—Changes in the Thyroid Activity During Treatment of Euthyroid Patients

Direction of Change	Changes in Mentation	
	Improved	Not Improved
No change	7	3
Changes inside the normal range	57	15
Change to hypofunctional range	12	7
Change to hyperfunctional range	5	1