described. Fifteen had consistently negative Rose-Waaler tests. Three had psoriasis, the remaining 13 being free from skin or nail lesions.

One patient had an erosive arthritis with predominant terminal interphalangeal-joint involvement, absence of psoriasis, and negative Rose-Waaler tests. It is thought that this case is an example of psoriatic arthritis without psoriasis.

Four patients, only one of whom had psoriasis, had radiological features suggestive of psoriatic arthritis.

Criteria are presented to enable the diagnosis of psoriatic arthritis to be made in the absence of psoriasis.

Although the remaining patients had a joint disease clinically and radiologically indistinguishable from rheumatoid arthritis, all but one had consistently negative Rose-Waaler tests and none had subcutaneous nodules of rheumatoid type.

The importance of seeking a family history of psoriasis and of making a thorough examination for psoriasis in patients with sero-negative polyarthritis of undetermined aetiology is stressed.

The presence of even trivial psoriasis is important in patients with arthritis in view of the dangers of chloroquine therapy in this skin disease.

We are indebted to Professor J. T. Ingram and Dr. G. Holti for their encouragement and for permission to study some of the patients.

REFERENCES

- Avila, R., Pugh, D. G., Slocumb, C. H., and Winkelmann, R. K. (1960). *Radiology*, **75**, 691.
 Baer, R. L., and Witten, V. H. (1962). *The Year Book of Dermatology*, 1961-62, p. 222. Year Book Publishers, Chicago.
 Baker, H., Golding, D. N., and Thompson, M. (1963). *Ann. int. Med.*, **58**, 909.
 Ball, J. (1952). *Ann. rheum. Dis.*, **11**, 97.
 Bauer, W., Bennett, G. A., and Zeller, J. W. (1941). *Trans. Ass. Amer. Phycns*, **56**, 349.
 Bremner, J. M., Alexander, W. R. M., and Duthie, J. J. R. (1959). *Ann. rheum. Dis.*, **18**, 279.
 Cornbleet, T. (1956). *J. invest. Derm.*, **26**, 435.
 Dawson, M. H., and Tyson, T. L. (1938). *Trans. Ass. Amer. Phycns*, **53**, 303.
 Dixon, A. St. J. (1960). *Ann. rheum. Dis.*, **19**, 209.
 — and Lience, E. (1961). *Ibid.*, **20**, 247.
 Fawcitt, J. (1950). *Brit. J. Radiol.*, **23**, 440.
 de Forest, G. K., Mucci, M. B., and Boisvert, P. L. (1956). *Amer. J. Med.*, **21**, 897.
 Gibson, H. J. (1948). In *Textbook of the Rheumatic Diseases*, edited by W. S. C. Copeman, p. 409. Livingstone, Edinburgh.
 — and Ling, N. R. (1956). *Ann. rheum. Dis.*, **15**, 246.
 Hoede, K. (1957). *Hautarzt*, **8**, 433.
 Ingram, J. T. (1954). *Brit. med. J.*, **2**, 823.
 Kellgren, J. H., and Ball, J. (1959). *Ibid.*, **1**, 523.
 Lawrence, J. S., and Ball, J. (1958). *Ann. rheum. Dis.*, **17**, 160.
 — Laine, V. A. I., and de Graaff, R. (1961). *Proc. roy. Soc. Med.*, **54**, 454.
 Romanus, T. (1945). *Acta derm.-venereol. (Stockh.)*, **26**, Suppl. 12.
 Sherman, M. S. (1952). *J. Bone Jt Surg.*, **34A**, 831.
 Steinberg, A. G., Becker, S. W., jun., Fitzpatrick, T. B., and Kierland, R. R. (1951). *Amer. J. hum. Genet.*, **3**, 267.
 Wassmann, K. (1949). *Ann. rheum. Dis.*, **8**, 70.
 Weissenbach, R. J. (1938). *Arch. derm.-syph. (Paris)*, **10**, 13.
 Wright, V. (1956). *Ann. rheum. Dis.*, **15**, 348.
 — (1959). *Amer. J. Med.*, **27**, 454.
 — (1961). *Ann. rheum. Dis.*, **20**, 123.
 Ziprowski, L., Haim, S., and Bank, H. (1954). *Acta med. orient. (Tel-Aviv)*, **13**, 45.

URINARY WHITE-CELL EXCRETION AFTER IRON-SORBITOL-CITRIC-ACID

BY

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During studies on the action of iron-sorbitol-citric-acid complex ("jectofer") in patients with hypochromic anaemia it was established that about one-third of the iron administered intramuscularly was excreted within 24 hours in the urine (Wetherley-Mein *et al.*, 1962; Pringle *et al.*, 1962). Scott (1962) has noted a possible provocation of an infection of the urinary tract in one patient with anaemia after treatment with iron-sorbitol. Recently provocative tests for the diagnosis of latent pyelonephritis have been established by the measurement of urinary white-cell excretion rates before and after the intravenous administration of a pyrogen (Pears and Houghton, 1958, 1959) or intravenous prednisolone phosphate (Little and de Wardener, 1962). The latter authors also found that three patients developed an exacerbation of a urinary infection after the administration of prednisolone phosphate. These observations suggested that iron-sorbitol might provoke a cellular response in states of renal infection. For this reason the urinary white-cell excretion rates were measured before and after the intramuscular administration of iron-sorbitol complex to normal subjects, patients with chronic infection of the urinary tract, and patients with non-infective renal disease.

Material and Methods

The cellular excretion in the urine was studied before and after the intramuscular injection of iron-sorbitol in

10 healthy subjects, in nine patients with present or past evidence of infection of the urinary tract (Table I), and in five patients with other renal disorders (Table II). The diagnosis of infection of the urinary tract was based on a typical clinical history as well as on quantitative bacterial counts (McGeachie and Kennedy, 1962)—that is, a bacterial count of more than 100,000 organisms per ml.

Urine was collected direct into a sterile container for the three-hour period immediately prior to the injection of iron-sorbitol and for two periods each of three hours in sequence after the injection. The urinary non-squamous white-cell excretion rate was counted in a Neubauer chamber after centrifugation of the urine, and the white-cell excretion rate per hour was calculated. Bacterial counts were performed on all the specimens by the method of McGeachie and Kennedy (1963). Iron-sorbitol 25 mg. was injected intramuscularly in all cases. In some patients an additional test was performed using 100 mg. of iron-sorbitol.

Results

The urinary white-cell excretion rates three hours before and three hours after the iron-sorbitol injection are shown in the Chart. In the 10 normal subjects the pre-injection urinary white-cell level ranged from 8,000 to 50,000 cells per hour and no significant alteration occurred after the injection of 25 mg. of iron-sorbitol. In 8 out of these 10 patients the test was repeated with 100 mg., again with

TABLE I.—*Clinical and Clinicopathological Findings in Nine Patients with Chronic Infection of the Urinary Tract. The Diagnosis of Infection of the Urinary Tract had been Previously Established in Each Patient on the Basis of a Bacterial Count of More Than 100,000/ml. The Urinary Bacterial Counts Noted in this Table were Performed at the Time of the Iron-sorbitol Test, when only in Case 5 was the Count Positive*

No.	Age	Sex	Duration of Symptoms	Symptoms	Intravenous Pyelogram	Urinary Bacteria (per ml.)	Present Therapy	Urinary White-cell Excretion (per Hour)	
								3-hour Period before Iron-sorbitol Injection	3-hour Period after Iron-sorbitol Injection
1	52	F	8 years	Dysuria and increased frequency of micturition	Ectopic kidney	<i>E. coli</i> : 6×10^4	None	4,400,000	9,800,000
2	25	F	8 months	Bilateral loin pain and dysuria; creatinine clearance 82 ml. min.	Normal	Negative	Nitrofurantoin 50 mg. t.i.d.	55,000	1,580,000
3	50	F	Several years	Dysuria and increased frequency of micturition	—	"	Sulphadimidine 0.5 g. b.d.	777,000	303,000
4	39	F	6 months	Right-sided loin pain	Normal	"	Nitrofurantoin 50 mg. t.i.d.	22,000	116,000
5	48	F	19 years	Loin pain and dysuria	Ptosis of right kidney	Paracolon bacilli: more than 10^8	Nitrofurantoin 50 mg. t.i.d.	3,670,000	1,430,000
6	52	M	3 months	Dysuria and haematuria	Normal	Negative	Nitrofurantoin 50 mg. t.i.d.	50,000	160,000
7	37	F	10 years	Dysuria and increased frequency of micturition; creatinine clearance 20 ml. min.	—	"	Nitrofurantoin 50 mg. t.i.d.	810,000	1,680,000
8	50	F	Several years	Dysuria and increased frequency of micturition	—	"	None	44,000	190,000
9	13	F	6 years	Bilateral loin pain and dysuria	Duplication of left renal pelvis and ureter	"	"	14,000	140,000

TABLE II.—*Clinical Features of Five Patients with Non-infective Renal Disease*

No.	Age	Sex	Diagnosis	Clinical State
1	15	M	Nephrotic syndrome	Symptoms of 4 years' duration; receiving prednisone treatment
2	23	M	Subacute glomerulonephritis	Blood-pressure 160/110 mm. Hg; blood urea 61 mg./100 ml.; receiving methylglucamine treatment for hypertension
3	23	M	" "	Blood-pressure 150/110 mm. Hg; blood urea 113 mg./100 ml.; receiving methylglucamine treatment
4	44	F	Acute glomerulonephritis	Recovery phase; proteinuria present; creatinine clearance 60 ml. min.
5	41	M	Polycystic kidneys	Blood-pressure 180/114 mm. Hg; blood urea 57 mg./100 ml.; receiving methylglucamine treatment

Urinary white-cell excretion rate, expressed as number of leucocytes per hour, and plotted logarithmically, during the three-hour periods before (A) and after (B) the intramuscular injection of 25 mg. of iron-sorbitol, in 10 normal subjects, nine patients with chronic infection of the urinary tract, and five patients with non-infective renal disease.

negative results. In the five patients with non-infective renal disease the pre-injection white-cell excretion ranged from 30,000 to 500,000 cells per hour. No significant alteration in these levels occurred after 25 mg. of iron-sorbitol. In two cases the test was repeated with 100 mg., again with no response. In the nine patients with chronic infection of the urinary tract the pre-injection white-cell excretion rates were much higher, ranging from

14,000 to 6,500,000 cells per hour. In seven of the nine patients the white-cell excretion rate rose by more than 100% after 25 mg. of iron-sorbitol. In the remaining two subjects there was no rise. In these two subjects the test was repeated, using 100 mg. of iron-sorbitol, but there was no significant rise in the white-cell excretion. A further patient with chronic infection of the urinary tract, who is not included in this series, showed a rise in the white-cell excretion rate of more than 100% following 100 mg. of iron-sorbitol, although she had previously shown no response after 25 mg. All the above results are based on the white-cell excretion rates three hours before and three hours after the iron-sorbitol injection.

The white-cell excretion rates for the three to six-hour period in the patients with chronic urinary infection who showed a response were variable; three rose slightly, while the remaining four fell. No alteration in the bacterial counts in the urine samples were observed after the administration of iron-sorbitol in patients of any of the three groups. In no patient was there any clinical evidence of a subsequent exacerbation of an infection of the urinary tract after the injection.

Discussion

The measurement of the urinary white-cell excretion rate before and after the intravenous administration of a pyrogen was described by Pears and Houghton (1958, 1959) as a method of establishing the diagnosis of chronic pyelonephritis in cases where urine microscopy and culture studies were negative or equivocal. The side-effects of this test may be very disturbing to the patient, and in an attempt to find a less unpleasant test Little and de Wardener (1962) described the use of prednisolone phosphate for the same purpose. An exacerbation of an infection of the urinary tract occurred in three patients in whom prednisolone was used in this way. In the present study seven out of the nine patients with a chronic infection of the urinary tract obtained a significant rise in the white-cell excretion rate after 25 mg. of iron-sorbitol. In the two patients who showed no response the clinical and bacteriological evidence of urinary infection was definite. It is, however, important to note that these two patients were among the five in the study who were on long-term chemotherapy at the time of the test.

The mechanism of the rise in the urinary white-cell excretion in these cases is of interest. Perhaps the most important point is the urinary excretion of about 33% of injected iron-sorbitol within a few hours. Wöhler (1962) has demonstrated in experimental animals that the iron-sorbitol complex crosses Bowman's capsule of the glomerulus, presumably because of the low molecular weight of the complex—namely, 5,000. Furthermore, this author has also shown that iron has a predisposition to localize in areas of infection. These findings may explain the provocation of white-cell excretion after iron-sorbitol in patients with a chronic infection of the urinary tract.

The results raise two questions. Firstly, is the intramuscular injection of iron-sorbitol an effective agent, comparable to intravenous pyrogen or prednisolone, in the diagnosis of latent states of chronic urinary infection? The fact that a significant rise, over 100%, in the urinary white-cell excretion occurred in seven out of nine cases suggests that this method is worthy of further consideration. In addition, iron-sorbitol is administered intramuscularly and, unlike pyrogen, no side-reactions occurred in any case.

A second question of importance is the relevance of these findings to the possible provocation of infection of the urinary tract after iron-sorbitol injections. This was noted by Scott (1962), although she could cite only a single patient. There was, however, no clinical deterioration in any of the present cases; nor was there evidence of an increase in the bacterial count. Furthermore, Walquist (1962) failed to find deterioration of renal function in patients with chronic renal disease given iron-sorbitol. Nevertheless, the fact that a significant urinary cellular increase was obtained in the majority of patients suggests that the association of an iron-sorbitol injection with a urinary infection noted by Scott (1962) was not entirely fortuitous. For this reason it may be a wise precaution to avoid the use of iron-sorbitol in patients with an active infection of the urinary tract.

Summary

The urinary white-cell excretion rate after the intramuscular injection of iron-sorbitol-citric-acid complex ("jectofer") was observed in 10 healthy subjects, in 9 patients with chronic infection of the urinary tract, and in 5 patients with other renal diseases. The white-cell excretion rate rose by more than 100% in seven of the nine patients, with infection of the urinary tract, while there was no significant rise in the other two groups.

This observation may be explained by the urinary excretion of iron-sorbitol to an extent of one-third of the intramuscular dose, as well as the known predisposition of iron to localize in infected tissues.

Iron-sorbitol, used in this way, may be of value in the diagnosis of chronic infection of the urinary tract.

A single case has been previously reported in which the injection of iron-sorbitol may have provoked an infection of the urinary tract.

For these reasons it is suggested that iron-sorbitol should not be administered to patients with an active urinary infection.

We would like to thank Dr. J. McGeachie for carrying out the bacterial counts.

Addendum

Since this paper was written the urinary white-cell excretion after the intramuscular injection of iron-sorbitol

has been studied in a further group of 33 patients. Twelve suffered from non-infective renal disease and in 11 of these there was no significant alteration in the white-cell excretion after the injection. The one patient who showed a rise in white-cell excretion of more than 100% after the injection had the clinical features typical of focal glomerulonephritis.

The remaining 21 patients had proved infection of the urinary tract of whom three were on treatment at the time of the test. In 13 patients the white-cell excretion rate rose by more than 100% after the injection, while in eight there was no significant alteration. Two of these eight patients were on treatment at the time of the test.

Of the 30 patients therefore in the complete series with proved infection of the urinary tract 20 showed a rise of more than 100% in the urinary white-cell excretion rate after the intramuscular injection of iron-sorbitol. In none of these additional patients was there any evidence of untoward effects from administration of the iron.

REFERENCES

- Little, P. J., and de Wardener, H. E. (1962). *Lancet*, **1**, 1145.
 McGeachie, J., and Kennedy, A. C. (1963). *J. clin. Path.*, **16**, 32.
 Pears, M. A., and Houghton, B. J. (1958). *Lancet*, **2**, 128.
 — (1959). *Ibid.*, **2**, 1167.
 Pringle, A., Goldberg, A., Macdonald, E., and Johnston, S. (1962). *Ibid.*, **2**, 749.
 Scott, Jean M. (1962). *Brit. med. J.*, **2**, 480.
 Wahlquist, S. (1962). Symposium on Jectofer organized by Astra Pharmaceutical Products Inc. September, 1962, at Worcester, Mass., U.S.A.
 Wetherley-Mein, G., Buchanan, J. G., Glass, U. H., and Pearce, L. C. (1962). *Brit. med. J.*, **1**, 1796.
 Wöhler, F. (1962). Symposium on Jectofer organized by Astra Pharmaceutical Products Inc. September, 1962, at Worcester, Mass., U.S.A.

IRON-SORBITOL-CITRATE IN PREGNANCY ANAEMIA

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During pregnancy parenteral-iron therapy is invaluable in the treatment of iron-deficiency anaemia, especially in patients near term. Thus when Richmond (1959, 1960) and Haddow and Horning (1960) published their findings on the induction of sarcoma at injection sites in rats and mice after massive doses of iron dextran ("imferon") it was natural that other intramuscular preparations should be sought, no matter how remote the clinical application of these animal experiments. Iron-sorbitol-citric-acid complex ("jectofer") appeared to be a suitable alternative, and it had already been used to advantage in non-pregnant patients (Andersson, 1961) when the present trial was undertaken.

Materials and Methods

The majority of patients reviewed received treatment at the antenatal blood clinic, held thrice weekly. At their first visit a full blood count, including reticulocytes, was made and blood films and buffy coats were screened. The marrow was also examined in some patients. Haemoglobin estimations were made on an EEL colorimeter, and reticulocyte counts were done daily in hospital patients or at each clinic visit in the others. Repeat blood counts were carried out at weekly intervals.

This regime was the same as that adopted in an earlier trial with imferon (Scott, 1956) except that less iron could be administered with each injection, as the recommended