THE USE OF OXYTETRACYCLINE IN PREVENTING OR DELAYING ISONIAZID RESISTANCE IN PULMONARY TUBERCULOSIS

A REPORT TO THE RESEARCH COMMITTEE OF THE TUBERCULOSIS SOCIETY OF SCOTLAND*

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The frequent emergence of drug-resistant tubercle bacilli in patients treated with streptomycin, with salts of *p*-aminosalicylic acid (P.A.S.), or with isonicotinic acid hydrazide (isoniazid) alone is now common knowledge (Dye *et al.*, 1953; Medical Research Council, 1948, 1950, 1952, 1953b). Following reports of the use of oxytetracycline ("terramycin") alone in patients suffering from pulmonary tuberculosis (Pfefer *et al.*, 1952; Söderholm, 1952) a number of workers (Des Autels, 1953; Miller *et al.*, 1952, 1953; Pfefer *et al.*, 1952; Rothstein and Johnson, 1952) investigated the effect of oxytetracycline in reducing the incidence of streptomycin resistance. The present report deals with the use of oxytetracycline in delaying or preventing the onset of isoniazid resistance.

Material

In the original series of Miller *et al.* (1952) treated with streptomycin and oxytetracycline, the latter was given in a dose of 5 g. daily. Ten patients in the present series were treated with this dose. In all of these the tubercle bacilli were already resistant to streptomycin or P.A.S., or to both. It was hoped by the combination of isoniazid and oxytetracycline to make a desperate case fit for surgery. It was later realized that, in view of the expense involved, a smaller dose of oxytetracycline would be desirable if it were effective. Consequently in a second series of 23 patients the oxytetracycline was given in a daily dose of 1 or 2 g., the patients being allotted to the 1-g. or 2-g. group according to a table of random numbers. It should be emphasized that the first series, given 5 g. daily, was not allotted in this way. In all except five of those given isoniazid with 1 or 2 g. of oxytetracycline daily, the bacilli were already resistant to streptomycin or P.A.S., or to both. In the five whose bacilli were sensitive the disease was of such extent and chronicity that only a limited response could be expected to any form of treatment.

The emergence of isoniazid-resistant organisms in these patients was compared with that in a previous series of

patients with similar disease treated on isoniazid alone (Wallace *et al.*, 1954).

The treatment groups were as follows: (1) T1H group: oxytetracycline, 1 g. daily, in four doses of 0.25 g., plus isoniazid, 100 mg. twice a day. (2) T2H group: oxytetracycline, 2 g. daily in four doses of 0.5 g., plus isoniazid, 100 mg. twice a day. (3) T5H group: oxytetracycline, 5 g. daily, in four doses of 1.25 g., plus isoniazid, 100 mg. twice a day. (4) H group: isoniazid 100 mg. twice a day *alone*.

In all groups the minimum duration of treatment was three months.

In Table I are compared, for the different groups, pre-treatment radiographic appearances known to be associated with the emergence of drug resistance—namely, cavitation

TABLE I.—Degree of Cavitation and Confluence in the Pre-treatment Radiographs

Treatment Group	No. of Cases	Degree of Cavitation*				Degree of Confluence†			
		+++	++	+	Nil	+++	++	+	Nil
T1H	10	3	3	4	0	3	4	2	1
T2H	13	7	5	1	0	7	2	2	2
T5H	10	7	2	0	1	2	3	5	0
H	17	9	4	3	1	3	5	9	0

* Total diameters of cavities present: 5 cm. or above = + + +, 2-4.9 cm. = + +, less than 2 cm. = +.

† Shadows confluent over three-quarters or more of one zone = + + +, one-quarter to three-quarters of one zone = + +, less than one-quarter of one zone = +.

(Mitchell, 1949; Howard *et al.*, 1949; Howlett *et al.*, 1949) and confluence of shadows (Bignall *et al.*, 1950). It will be seen that the distribution is similar except that fewer patients in the T1H group had gross cavitation and more patients in the T2H group had grossly confluent shadows than in the other groups. As regards pre-treatment erythrocyte sedimentation rate (E.S.R.), shown in Table II, the H and

TABLE II.—Pre-treatment Erythrocyte Sedimentation Rates

Treatment Group	Total No. of Cases	E.S.R. (mm./hr. Westergren)			
		0-9	10-29	30-49	50 and Over
T1H	10	1	2	1	6
T2H	13	0	3	2	8
T5H	10	4	1	1	4
H	17	1	6	7	3

T5H groups tended to have lower levels than the other two groups. Too few patients were febrile for any useful comparison to be made between the groups. In general the patients in the trial had a chronic type of disease with moderate or gross cavitation. Most of them had previously received long courses of streptomycin and P.A.S., often in rhythms and doses now regarded as unsatisfactory, but none had had isoniazid.

Methods

The sputum was cultured on at least two occasions before the start of treatment and then at weekly intervals. Drug-sensitivity tests were carried out on the pre-treatment cultures and monthly thereafter. When resistance was encountered intermediate cultures were also tested in order to determine more accurately the time of onset of resistance. Cultures and isoniazid-sensitivity tests were performed by the methods recommended by the Medical Research Council (1953a). Isoniazid resistance was recorded as "sensitive" or as resistant to 0.2, 1, 5, 10, or 50 µg./ml. Cultures were considered to be resistant when 20 or more colonies were obtained on Löwenstein-Jensen slopes containing 0.2 µg. of isoniazid per ml. or above. In each case in which a culture resistant to 0.2 µg./ml. was obtained later cultures from the same patient showed a higher degree of resistance. For the oxytetracycline-sensitivity tests Dubos and Davis's (1946) liquid medium was used. The method was the same as that recommended by the Medical Research Council (1953a) for testing bacterial sensitivity to streptomycin,

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except that the readings were made after 12 days' incubation. All sensitivity tests were done by the same worker (S. M. S.).

Chest radiographs were taken monthly and radiographic assessments were made by an independent panel. The sedimentation rate and weight were also recorded monthly, and a note was made of the average evening temperature for the seven days preceding each monthly review. Symptoms attributable to drug toxicity were recorded at each monthly examination.

Results of Isoniazid-Resistance Tests

The results of the sputum examinations are shown in Table III. Within six months of starting treatment isoniazid-resistant organisms were isolated from 5 of the 10 patients

TABLE III.—*Bacteriological Results at End of Three Months' Treatment and Any Subsequent Development of Isoniazid Resistance*

Treatment Group	No. of Cases	No. of Cases at 3 Months			No. of Cases in which Isoniazid Resistance was First Demonstrated Later than 3 Months*	Total No. Isoniazid-resistant by 6 Months
		Sputum Negative	Sputum Positive and Isoniazid-sensitive	Sputum Positive and Isoniazid-resistant		
T1H ..	10	5	1	4	1 (3‡)	5
T2H ..	13	6	4	3	2 (4), 1 (6)	6
T5H ..	10†	5	4	0	2 (5), 1 (15)†	2
H ..	17	6	0	11	1 (5)	12

* The figures in parentheses give the duration of treatment in months before the first isolation of isoniazid-resistant organisms.

† One patient had an isolated positive culture, but no growth was obtained on the sensitivity test. The sputum subsequently became negative until the fifteenth month of continuous treatment, when a resistant culture was obtained.

in the T1H group, from 6 of the 13 in the T2H group, from 2 of the 10 in the T5H group, and from 12 of the 17 in the H group. In addition, in the T5H group, a single positive culture resistant to isoniazid was obtained from one of the patients after 15 months of continuous treatment.

Isoniazid Resistance Emerging Within Three Months of Starting Treatment

From Table III it will be seen that of the five positive cultures at three months in the T1H group, four were resistant to isoniazid; of the seven positive cultures in the T2H group, three were resistant. In the T5H group none of the four positive cultures was isoniazid-resistant. All eleven positive cultures from the group on isoniazid alone were resistant. Sputum conversion occurred in about one-half of the cases in each of the groups given oxytetracycline. In about one-third of the group given isoniazid alone the sputum was negative on culture. In all treatment groups in which sputum conversion occurred the last positive culture was sensitive to isoniazid.

Isoniazid Resistance Emerging Later than Three Months after Starting Treatment

Resistance was first demonstrated later than the third month of treatment in eight of the cases (Table III). Of those who were sputum-negative at three months, resistant bacilli were subsequently isolated from one of the five patients in the T1H group, from two out of the six in the T2H group, from none in the T5H group, and from one of the six patients in the H group. Of those patients whose organisms were sensitive at the end of the third month of treatment, isoniazid resistance was later demonstrated in only three. In one, in the T2H group, resistant bacilli were isolated after four months' treatment. In the remaining two, in the T5H group, resistant organisms were isolated only after five months' treatment. In one other patient in the T5H group bacilli failed to grow in the sensitivity test performed after three months' treatment; after 15 months' continuous treatment an isolated culture was obtained which was resistant to isoniazid.

Details are as follows:

T1H Group.—Five cases were sputum-negative at three months. Of these, three were treated for three, four and a half, and five

months respectively, at the end of which time they were still sputum-negative. In two thoracoplasty was carried out, and the third had a pneumonectomy. A fourth patient who had six months' treatment remained sputum-negative for a further period of three months. Subsequently the sputum became positive and the organisms were sensitive to isoniazid. The fifth patient had a pneumonectomy three and a half months after starting treatment. She had been sputum-negative from the 77th day of treatment, but cultures from the lung were resistant to isoniazid. The only patient in this group who was sputum-positive and whose organisms were sensitive to isoniazid at three months changed treatment after completing three months' oxytetracycline and isoniazid.

T2H Group.—Of the six cases sputum-negative at three months, two were treated for five and six months respectively and remained sputum-negative. A third case was treated for three months only. A positive culture was obtained three months later and the organisms were sensitive to isoniazid. Two cases remained sputum-negative until the end of the fourth and fifth month of treatment respectively. In both cases isoniazid-resistant organisms were then isolated from the sputum. The sixth case received oxytetracycline and isoniazid for three months only. He was then given P.A.S. and isoniazid. There were four patients from whom isoniazid-sensitive organisms were isolated at the end of three months' treatment. Two became sputum-negative by the end of the fourth month of treatment. One of these completed six months' treatment and remained sputum-negative. The other has received only four months' treatment so far. A further case has received five months' treatment. Isoniazid-sensitive organisms were isolated at four months, but the sputum was negative by the end of the fifth month. In the last case isoniazid-resistant organisms were isolated at the fourth month.

T5H Group.—Five patients were sputum-negative at three months. In one of these the sputum remained negative throughout five months of treatment. A left upper lobectomy was then performed; cultures from the lung lesions were sensitive to isoniazid. In a second patient who had nine months' treatment a single positive culture obtained at the sixth month was sensitive to isoniazid. The other three have completed only three to four months' treatment, and have so far remained sputum-negative. Five patients were sputum-positive at the end of three months' treatment. Two were negative by the fourth month. One of these subsequently had a thoracoplasty. In the second the sputum was negative up to the eighth month of treatment, when a right upper lobectomy was performed. Cultures on the material from the lung lesions were negative and inoculation into guinea-pigs produced only local glandular enlargement. Isoniazid-sensitivity tests are not yet available on the organisms from these lesions. In two patients who received over five months' treatment isoniazid-sensitive organisms were isolated at the fourth month, but resistant organisms were isolated at the fifth month. The fifth patient's sputum was positive after three months' treatment, but the bacilli failed to grow in the sensitivity test. Subsequently, weekly cultures were negative until, after fifteen months' continuous treatment, a single positive culture was obtained which proved resistant to isoniazid.

H Group.—Six cases were sputum-negative at three months. Two of these received isoniazid for six months and remained sputum-negative throughout treatment; one has remained sputum-negative for a subsequent twenty-two months off treatment; in the other, chemotherapy was changed at the end of the course of isoniazid. Two cases completed six months' isoniazid and remained sputum-negative after the end of treatment for three and four months respectively. Positive cultures obtained at these times were sensitive to isoniazid. A fifth case treated for six months remained sputum-negative until the fifth month, when isoniazid resistant organisms were isolated. In the sixth case chemotherapy was changed after three months' isoniazid. There were no patients in this group who were sputum-positive and whose organisms were sensitive to isoniazid after three months.

Oxytetracycline Sensitivity

Owing to the low incidence of oxytetracycline resistance in pulmonary tuberculosis so far reported, no definite criteria of resistance have yet been established. The results in the present series, shown in Table IV, suggest that no rise of resistance has occurred after three months' treatment. Oxytetracycline-resistance tests were available at four months on cultures from 11 patients, at five months from 9 patients, at six months from 5 patients, and at nine months from 1 patient. In no case was the resistance ratio greater than that found on the pre-treatment culture.

TABLE IV.—Results of the Oxytetracycline-sensitivity Tests, Expressed as the Inhibitory Concentration in $\mu\text{g./ml.}$ and as a Resistance Ratio Compared with the Standard H37Rv Strain, on the Pre-treatment Cultures and on those Isolated after Three Months' Treatment on 32 Patients

Treatment Group	Results on Pre-treatment Cultures							Results on Cultures Isolated after 3 Months' Treatment								
	Total No. Tested	Inhibitory Conc., $\mu\text{g./ml.}$			Resistance Ratio			Total No. Tested	Inhibitory Conc., $\mu\text{g./ml.}$				Resistance Ratio			
		1	2	4	$\frac{1}{4}$	$\frac{1}{2}$	1		1	2	4	8	$\frac{1}{4}$	$\frac{1}{2}$	1	
T1H..	10	2	2	6	2	3	5	5	3	0	2	0	3	0	2	
T2H..	13	3	8	2	3	8	2	7	3	3	1	0	2	4	1	
T5H..	9	3	4	2	3	4	2	4	0	2	1	1	0	2	2	
Total	32	8	14	10	8	15	9	16	6	5	4	1	5	6	5	

Clinical Progress.—This was assessed by the objective methods already detailed. There was no important difference between the groups after three months of treatment.

Toxic Effects Attributable to Oxytetracycline

Diarrhoea was noted in 2 cases of the T1H group, in 4 of the T2H group, and in 4 of the T5H group. In 3 of the 10 patients it was transient, occurring only over the first month. In only 2 of the 10 was the diarrhoea of any severity, but even in these it was not sufficient to interfere with therapy. Anorexia and slight vomiting occurred in four cases, but required no treatment. One case originally admitted to the T5H group had to be removed from the trial within the first week of treatment owing to intractable vomiting and diarrhoea. This case, therefore, is not included in any of the results. One case in the T2H group developed pruritus of the legs over the first three days of treatment; this was relieved by antihistamine drugs.

Discussion

It has been shown by Pfefer *et al.* (1952) and by Söderholm (1952) that oxytetracycline when used alone has little to offer in the treatment of pulmonary tuberculosis. When used in combination with streptomycin, however, the incidence of resistance to streptomycin can be greatly reduced (Des Autels, 1953; Miller *et al.*, 1952, 1953; Pfefer *et al.*, 1952; Rothstein and Johnson, 1952). When isoniazid is given with streptomycin or P.A.S., the incidence of drug resistance is markedly lowered, provided that the patient's organisms are fully sensitive at the start of treatment (Dye *et al.*, 1953; Medical Research Council, 1953b, 1953c; Pitts *et al.*, 1953). Both these combinations are now widely used, and with great success. Nevertheless there are a few patients whose organisms are resistant to streptomycin and P.A.S. owing either to previous unsatisfactory chemotherapy or to infection with resistant organisms (Thomas *et al.*, 1954). For such patients isoniazid is the only effective drug left, and it would be of great value to have a fourth drug which could be used to delay or prevent the onset of isoniazid resistance. The possible value of oxytetracycline for this purpose is examined in the present study. As the series consisted of patients who were thought likely to remain sputum-positive it was possible to obtain bacteriological results of negative value even from small groups.

There was no difference between the progress of the patients receiving oxytetracycline and isoniazid and those receiving isoniazid alone. Therefore no clinical evidence was found of the antagonism between these drugs that has been demonstrated in the laboratory (Mackness and Smith, 1953). The object of using oxytetracycline was of course the hope that this drug would inhibit multiplication of the small number of isoniazid-resistant mutants which occur in any population of tubercle bacilli, and which in the presence of isoniazid may ultimately replace the sensitive organisms.

From the results shown in Table III it can be seen that in each of the oxytetracycline and isoniazid treatment groups sputum conversion occurred in approximately one-half of the cases by the end of the third month of treatment. In the isoniazid group this occurred in about one-third. The numbers in each group are small and the difference in the conversion rate is possibly due to chance.

There is no great difference in the incidence of isoniazid resistance in the H and T1H treatment groups, resistance having occurred in 11 of the 17 patients in the H group at the end of three months' treatment, compared with 4 out of 10 in the T1H group. In the T2H group isoniazid-resistant organisms occurred in only 3 of the 13 patients at the end of three months' treatment. Resistant bacilli were later found in 3 of the 10 patients in this group who were sputum-negative or whose organisms were still sensitive to isoniazid after three months' treatment, as compared with one of the six patients in the H group. Therefore in this small series, although isoniazid resistance developed less often in the T2H group than in the H group, the difference might well be due to chance. Neither T1H nor T2H can be recommended as satisfactory treatment regimes owing to the considerable incidence of isoniazid resistance in both groups.

Only 10 cases were treated with T5H, and therefore the results, though suggestive, need further confirmation. Although isoniazid resistance emerged in three of the cases, it occurred in none before the fifth month of treatment. In two, resistant bacilli were isolated at the end of the fifth month, and in the third only after fifteen months' continuous treatment, in spite of weekly cultures. These results suggest that by using oxytetracycline in a dose of 5 g. daily with isoniazid the period of effective chemotherapy—that is, the time before the emergence of isoniazid resistance—is likely to be considerably longer than with isoniazid alone or with T1H or T2H.

No oxytetracycline resistance was encountered in any of the treatment groups.

Although one case had to be removed from the trial within the first week of treatment with T5H because of severe vomiting and diarrhoea, in general the toxic effects of oxytetracycline were slight and did not prevent the continuation of treatment. Diarrhoea tended to occur within the first month, but generally it ceased spontaneously thereafter. The incidence of anorexia, vomiting, and diarrhoea was less than that reported by Miller *et al.* (1952, 1953), and no glossitis or cheilosis was seen.

It is probable that oxytetracycline, even in doses of 5 g. a day, is less effective than streptomycin or P.A.S. in delaying or preventing the emergence of isoniazid resistance. If oxytetracycline is to be used it is probably of little value at a lower dose than 4 to 5 g. a day, at least if given in four divided doses as in our series. At present prices the ratio of the cost of 5 g. of oxytetracycline with 200 mg. of isoniazid daily to 1 g. of streptomycin with 20 g. of sodium P.A.S. daily is 11 to 1. The use of oxytetracycline in preventing isoniazid resistance should therefore be restricted to the very few cases in which no other effective chemotherapy is available. Its principal value will probably lie in the preparation for radical surgery of patients whose organisms are resistant to both streptomycin and P.A.S. In fact, of the 10 cases in this series treated with isoniazid and 5 g. of oxytetracycline daily no fewer than five otherwise hopeless cases were made fit for surgery and now appear to have a relatively good prognosis.

Summary

Thirty-three cases of pulmonary tuberculosis were treated with oxytetracycline and isoniazid. Oxytetracycline was given in a dose of 1 g. daily (T1H) to 10 patients, 2 g. daily (T2H) to 13 patients, and 5 g. daily (T5H) to 10 patients. A group of 17 patients with similar disease, who had been treated with isoniazid alone (H group), was used for the purposes of comparison.

Sputum conversion occurred by the end of the third month of treatment in 5 of the 10 patients in the T1H group, in 6 of the 13 in the T2H group, and in 5 of the 10 patients in the T5H group. Six of the 17 patients in the H group had become sputum-negative over the same period.

Isoniazid-resistant organisms were isolated at some time from about one-half the patients in the T1H and the T2H groups and from about two-thirds in the H group; but in the T5H group resistant organisms were obtained from only 3 out of the 10 patients, and in none before the end of the fifth month of treatment.

No oxytetracycline resistance was encountered.

There was no important difference between the four treatment groups as regards clinical or radiological progress over the first three months of treatment.

Treatment of one patient in the T5H group had to be stopped after one week because of intractable diarrhoea and vomiting. Apart from this, the toxic effects attributable to oxytetracycline were slight.

Owing to the considerable incidence of isoniazid resistance in the T1H and T2H groups, neither method can be recommended as satisfactory in treatment. On the other hand, oxytetracycline in a dosage of 5 g. daily would seem to be of probable value in delaying or preventing the onset of isoniazid resistance, but this combination is likely to be less effective than that of streptomycin or P.A.S. with isoniazid; it is also very expensive.

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ADDENDUM.—Since this paper was submitted for publication the patients reported above, and three additional patients in the T5H group, have completed a minimum of six months' clinical and bacteriological observation. The one exception was a patient in the T5H group who discharged himself from hospital after three months; the remainder of the cases in the T5H group completed six months' treatment. The figures for isoniazid resistance within six months of starting treatment (three-month figures in parentheses) are now: for isoniazid alone, 12 (11) out of 17; T1H, 5 (4) out of 10; T2H, 7 (3) out of 13; and T5H, 2 out of 12 (0 out of 13 at three months). The difference between the H and T5H figures at three months is statistically significant ($P < 0.01$). No oxytetracycline resistance was encountered.

REFERENCES

- Bignall, J. R., Clegg, J. W., Crofton, J. W., Smith, B. J. D., Holt, H. D., Armitage, P., and Mitchison, D. A. (1950). *British Medical Journal*, **1**, 1224.
- Des Autels, E. J. (1953). *Transactions of the 12th Conference on the Chemotherapy of Tuberculosis*, p. 304. Veterans Administration, United States of America.
- Dubos, R. J., and Davis, B. D. (1946). *J. exp. Med.*, **83**, 409.
- Dye, W. E., Lynch, Helen P., and Brees, Atlanta G. (1953). *Amer. Rev. Tuberc.*, **67**, 106.
- Howard, W. L., Maresh, F., Mueller, E. E., Yannitelli, S. A., and Woodruff, C. E. (1949). *Ibid.*, **59**, 391.
- Howlett, K. S., jun., O'Connor, J. B., Sadusk, J. F., jun., Swift, W. E., jun., and Beardsley, F. A. (1949). *Ibid.*, **59**, 402.
- Mackness, G. B., and Smith, N. (1953). *Ibid.*, **67**, 322.
- Medical Research Council (1948). *British Medical Journal*, **2**, 769.
- (1950). *Ibid.*, **2**, 1073.
- (1952). *Ibid.*, **2**, 735.
- (1953a). *Lancet*, **2**, 213.
- (1953b). *British Medical Journal*, **1**, 521.
- (1953c). *Ibid.*, **2**, 1005.
- Miller, F. L., Sands, J. H., Gregory, L. J., Hightower, J. A., Weiser, O. L., and Tempel, C. W. (1953). *Transactions of the 12th Conference on the Chemotherapy of Tuberculosis*, p. 356. Veterans Administration, United States of America.
- Walker, R., Dye, W. E., and Tempel, C. W. (1952). *Amer. Rev. Tuberc.*, **66**, 534.
- Mitchell, R. S. (1949). *New Engl. J. Med.*, **241**, 450.
- Pfeifer, L. M., Hughes, F. J., and Dye, W. E. (1952). *Dis. Chest*, **21**, 123.
- Pitts, F. W., Tempel, C. W., Miller, F. L., Sands, J. H., Fitzpatrick, M. J., Weiser, O. (1953). *J. Amer. med. Ass.*, **152**, 886.
- Rothstein, E., and Johnson, M. P. (1952). *Transactions of the 11th Conference on the Chemotherapy of Tuberculosis*, p. 59. Veterans Administration, United States of America.
- Söderholm, B. (1952). *Acta tuberc. scand.*, **27**, 109.
- Thomas, O. F., Borthwick, W. M., Horne, N. W., and Crofton, J. W. (1954). *Lancet*, **1**, 1308.
- Wallace, A. T., Stewart, Sheila M., Turnbull, F. A. W., and Crofton, J. W. (1954). *Tubercle (Lond.)*, **35**, 164.

TREATMENT OF HAEMOCHROMATOSIS BY REPEATED VENESECTION

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Repeated venesection is now being used in the treatment of haemochromatosis (Davis and Arrowsmith, 1953; Houston, 1953; Warthin *et al.*, 1953). It has been found that appreciable amounts of iron may be mobilized for haemoglobin formation in response to venesection and that the total amount of blood which can be removed without the development of anaemia is chiefly dependent on the available body iron store (S. Finch *et al.*, 1950). In haemochromatosis it is hoped by repeated bleeding to remove some of the enormous excess of iron deposited in the tissues and thereby halt the accompanying fibrosis and the clinical changes of the disease. The employment of venesection as a means of mobilizing the deposited iron in haemochromatosis is based mainly on theoretical considerations, and was first proposed by Balfour *et al.* (1942) and later by Schwartz and Blumenthal (1948) and by Granick (1949). The possible therapeutic use of venesection, however, is suggested by the rarity and late onset of haemochromatosis in women, in whom loss of iron through menstruation, pregnancy, and lactation is believed to suppress or delay the clinical expression of the disease (Houston, 1953).

A case of haemochromatosis, proved by skin biopsy and estimation of the serum iron and unsaturated iron-binding capacity (Houston and Thompson, 1953), has been treated by repeated venesection. During a period of two years 55 pints (31 litres) of blood, equivalent to approximately 15 g. of iron, have been removed. A severe anaemia developed at the end of this time and was preceded by a fall in serum iron, which suggested that the available body-iron stores had been exhausted. In spite of the anaemia, a definite improvement has been noted in the patient's condition.

Case Report

A man aged 55 came under observation in October, 1950, complaining of upper abdominal pain for two years, and increasing tiredness and pigmentation of the face for six months. He gave no family history suggestive of haemochromatosis and had had no previous illnesses other than an operation for duodenal ulcer in 1936. He had regularly drunk 6 to 8 pints (3.4 to 4.5 litres) of beer daily. On examination there was a marked grey-black pigmentation of the face, neck, and forearms, and the liver was enlarged and very tender, with a firm smooth edge palpable 4½ in. (12 cm.) below the right costal margin. The spleen was not felt, but free fluid was found in the abdomen, the abdominal girth being 44 in. (112 cm.). Examination of the urine revealed a mild glycosuria, but the liver-function tests and the blood count were completely normal. The diagnosis of haemochromatosis was established by skin