Discussion

There is a high incidence of raised serum-iron levels, diabetes, cirrhosis, and occasionally pigmentation in the siblings of haemochromatotic patients. Bothwell *et al.* (1959) report 107 siblings, of whom half were affected. Finch and Finch (1955) found that 20% of relatives had raised serum-iron level, and Debré *et al.* (1952) have reported a similar incidence. The exact mode of inheritance in this disorder has been difficult to discern, however.

According to Neel and Schull's (1954) thesis, idiopathic haemochromatosis is a familial disorder due to an autosomal gene which is transmitted as a Mendelian dominant, though with incomplete penetrance. Bothwell *et al.* believe that there is not only incomplete penetrance but also variable expressivity. The family reported here is interesting not only because of the consanguinity of the parents, but because neither parent showed any of the usual stigmata of the disease during life. There seems, therefore, no reason why the inheritance should not be through an autosomal recessive gene. Debré *et al.* (1958) in Paris believe that the increased rate of iron absorption characteristic of haemochromatosis may be determined by a single gene. When inheritance is homozygous an uncommon and fulminating type of haemochromatosis may result. In the heterozygous state a milder form is seen, with later onset of symptoms and signs. This is certainly in keeping with the clinical features of the family reported here. Some inquiry into the family pedigree and investigation of the relatives is clearly most important in this disease, and may often reveal both clinical and subclinical cases.

Summary

A family is described in which two siblings have haemochromatosis and another has a raised serum iron. The parents were related, the patient's mother having married an uncle.

The disorder is probably transmitted by an autosomal recessive gene.

The importance of examining a patient's relatives in tracing subclinical cases is emphasized.

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CONTROLLED TRIAL OF "VIRUGON" IN TREATMENT OF MEASLES

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We were interested in the claim that N¹,N¹-anhydrobis (β -hydroxyethyl) biguanide hydrochloride (A.B.O.B.) is an effective and non-toxic antiviral agent. It is marketed in this country in combination with the solanaceous alkaloids atropine methonitrate and scopolamine methonitrate, which are thought to have a synergistic effect, under the trade name of "virugon." Several workers believe that it is of value in the prevention (Bateson, 1960; Bohmansson, 1960; Haglind, 1960; Sandahl and Sjöberg, 1960; Sjöberg, 1960a) and treatment (Stenkula, 1959; Sjöberg, 1960a, 1960b) of influenza.

There is evidence that A.B.O.B. administration reduces the mortality in young hamsters injected intracerebrally with measles virus (Farquhar, 1960). Moreover, during an outbreak of measles 21 (24%) out of 88 patients on placebo tablets developed the disease but only 11 (12%) out of 90 patients on A.B.O.B. were affected. However, A.B.O.B. did not seem to affect the severity of the measles in the cases in which it occurred. But it could be argued that A.B.O.B. prevented the occurrence of the very mild cases of measles and reduced the severity of the potentially severe cases to average level.

Farquhar (1960) also quotes a "double-blind" trial of A.B.O.B. in the treatment of children with measles in which no significant difference was noted between the two groups. However, there were only five treated children and five controls in this investigation, and the tablets were not given until approximately one day after the rash appeared.

We decided to carry out a double-blind trial to see if virugon really was effective in the treatment of measles.

Method

During a period of six months, beginning in December, 1960, 41 patients with measles seen in our urban practice in North Liverpool were each given a bottle of tablets. The tablets contained either 100 mg. of virugon or a placebo. Each bottle was labelled with a code number, so that reference to a key, after the record card had been completed, enabled us to find whether

TABLE I.—Comparison of the Two Groups of Patients

	Virugon Series	Controls
Total No.	19	22
Sex ratio, males/females	13/6	11/11
Average age	4.6 years (S.D.=2)	4.1 years (S.D.=2)
	(Standard error of difference=0.63)	
No. with Koplik's spots	11 out of 19 (58%)	11 out of 21 (52%)
Time patients first seen and treatment begun:		
2 days before rash appeared . .	1	0
Day	2	2
„ of onset of rash	13	14
„ after onset of rash	3	6

the patient had received virugon or the dummy tablets. The mother was instructed to give the child one tablet three times a day, or in the case of children under 3 half a tablet three times a day. Subsequent analysis revealed that 19 patients received virugon and 22 inert tablets. In all cases treatment was begun on the day on which the patient was first seen. In the great majority it was on the day of onset of the rash (Table I).

In addition to the trial tablets the patient was given whatever treatment we would normally have prescribed. This usually included an aspirin preparation (average dose, $2\frac{1}{2}$ gr. (0.16 g.) q.i.d.) and a cough mixture. Patients with chest signs or otitis media, children with a history of "catarrh" or susceptibility to chest infection, and those who were very ill were generally given a sulphonamide (usually sulphadimidine suspension *B.N.F.*; average dose, 2 dr. (8 g.) stat. then 1 dr. (4 g.) t.d.s.) or oral penicillin (usually 125 mg. of phenoxymethylpenicillin t.d.s.). Four of the virugon group and three controls were given sulphonamides. Of the five patients in the virugon series treated with penicillin one received sulphonamide simultaneously and another, who developed pneumonia, was later given oxytetracycline instead. Six of the controls had penicillin. One patient on virugon was given oxytetracycline from the onset.

One of us made the clinical assessment in most cases. Although the other partners treated some cases, any subjective error would tend to be eliminated as each doctor saw cases in both groups. Also comparison of records made by the different observers showed very similar patterns, so we are satisfied that the participation of more than one doctor has not reduced the reliability of the findings.

Results

The 19 cases treated with virugon and the 22 cases given inert tablets appeared to be comparable, despite there being a higher proportion of males in the virugon series and a slight difference in average age. During the early stages the results suggested that virugon produced a more rapid fall in temperature and a quicker

disappearance of the rash. However, as the series increased in size it became evident that there was no significant difference between the patients treated with virugon and the controls. The results are summarized in Tables II and III.

No fair conclusion can be drawn from the incidence of complications, and in any case most of these were noticed on the first visit—i.e., before treatment was started. Incidentally, this adds force to the argument that prophylactic antibacterial drugs are of little value in the treatment of measles.

One patient in the control series had nausea and vomited once. Apart from this no side-effects were observed. We did not inquire specifically for side-effects, nor stress unduly the experimental nature of the treatment. The absence of significant side-effects agrees with the observations of others (Almberg, 1959; Schersten, 1959; Heijbel and Magnusson, 1960; Holmqvist, 1960; Sandring, 1960; Sjöberg, 1960a), although Bateson (1960) reported nausea and vomiting in 10% of cases on a dose of only one tablet twice daily.

Conclusions

We were unable to demonstrate that virugon, given in the dosage mentioned, was of any value in the treatment of measles. However, the rash was present before treatment was started in 16 out of the 19 patients given virugon. It has been suggested that the drug interferes with the development of the virus within the host cells (Liu and Engle, 1960), and if this is true it might not be effective unless given at the onset of the disease or at least before the rash has appeared. But, as stated previously, Farquhar (1960) observed that children developing measles during prophylactic treatment were as ill as the untreated cases. We must therefore reluctantly conclude that there is as yet insufficient evidence to justify the claim that virugon is of value in the treatment of children with measles even though it may be of use in the prevention of this condition.

Summary

Forty-one cases of measles were studied, using a double-blind technique, to assess the value of virugon in the treatment of children with measles.

The drug did not demonstrably influence the course of the disease.

No side-effects were observed.

We thank Bayer Products for supplying the tablets and record cards used in this trial.

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TABLE II

	Virugon Series	Controls
General assessment of response:		
Unsatisfactory	3 (16%)	2 (9%)
Satisfactory	12 (63%)	10 (48%)
Good	4 (21%)	9 (43%)
Complications	3 chest signs (1 severe pneumonia), 3 otitis media, 1 febrile convulsion	6 chest signs (no serious chest complications), 3 otitis media

TABLE III

	Virugon Series			Controls			S.E. of Diff.
		No. of Readings	S.D.		No. of Readings	S.D.	
Average axillary temperature (°F.):							
1st day (day rash appeared)	100.87	15	1.47	100.82	13	1.45	0.55
2nd day	99.73	8	1.65	99.25	9	1.05	0.67
3rd	98.28	11	1.77	98.0	14	1.14	0.62
Duration of rash in days	4.16	18	1.3	4.27	18	1	0.38
Duration of bed rest in days	2.75	16	1.88	2.93	15	1.65	0.62
Duration of malaise in days	3.66	15	1.85	2.79	14	1.61	0.64
Average No. of visits	3.18	17	0.62	3.1	21	0.87	0.076
Total No. of cases		19			22		

India had 34 medical colleges in 1950. By 1960 their number had grown to 61, and another 15 colleges are to be opened by 1966 under the Third Five-year Plan.