age groups is, however, significantly greater than in the younger groups ($\chi^2=21.53$; df=6 ; P<0.001).

Table III shows the percentage of medical beds occupied by patients with intracranial vascular lesions. The number of beds occupied by chronic cases, those who have been in

TABLE III.—*Percentage of Medical Beds Occupied by Intracranial Vascular Lesions*

	Men		Women	
	Hospital A	Hospital B	Hospital A	Hospital B
All cases	1·47	2·13	3·07	4·08
Cases in hospital more than:				
2 weeks	0·51	1·26	1·53	2·62
4 ,, ...	0·26	0·73	0·93	1·87
6 ,, ...	0·18	0·45	0·59	1·26
8 ,, ...	0·14	0·29	0·37	1·01
10 ,, ...	0·10	0·17	0·27	0·77
12 ,, ...	0·06	0·14	0·17	0·59

hospital more than a given time, is also indicated. From this table can also be estimated the proportion of beds saved by transfer of cases after, say, three or four weeks to a special hemiplegic unit.

Discussion

It is surprising to find that less than 5% of patients with intracranial vascular lesions became chronic hospital patients, and these occupied only a small proportion of the total medical beds. Patients over 60, because of the high mortality in this group, were not especially liable to become chronic cases. In fact, it was the younger groups which provided the largest number of long-term cases, probably owing to their greater ability to survive grossly disabling lesions.

The most striking feature of this series was the extremely high death rate in the first few days after admission. The expectation of survival increased rapidly with the age of the lesion. Hospitals which accept early cases, particularly those with casualty departments where patients with sudden apoplexy are taken from the street, can expect a large intake, a high mortality, and a rapid turnover, with relatively few chronic survivors. Those which accept late cases will have a smaller intake, a low mortality, and a long average stay in hospital. For this reason the experience of some hospitals may differ considerably from the two which have been studied in this investigation. What the present series does show is that a generous acceptance of early cases is not necessarily followed by an accumulation of chronic hemiplegics.

There are good reasons why cerebrovascular accidents should be admitted to hospital as soon as they occur, irrespective of the age of the patient or other social factor. Rehabilitation must be started early if it is to prevent permanent disability from contractures (Rusk and Taylor, 1952). Old people must be forced to help themselves before they become reconciled to a life of bed-fast dependence. Such treatment is more effectively carried out in hospital than in the patient's own home. Denial of hospital facilities in these circumstances is likely to add to the number of helpless cases at large in the community, and in the long run actually increase the demand for their accommodation in beds for acute cases.

Summary

The hospital records of 239 cases admitted to hospital following cerebrovascular accidents have been examined.

Less than 5% remained in hospital more than three months. Patients over 70 were not especially liable to become chronic hemiplegics.

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VALUE OF SERUM IRON LEVELS IN ASSESSING EFFECT OF HAEMATINICS IN THE MACROCYTIC ANAEMIAS

BY

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The serum iron shows specific variations in different types of anaemia (Riecker, 1930 ; Powell, 1944 ; Laurell, 1947 ; Cartwright and Wintrobe, 1952). It is low when the cause is iron deficiency, infection, or malignancy. Higher values than normal usually occur in the macrocytic anaemias and in those due to haemolysis or hypoplasia of the bone marrow. Moore and Doan (1937) reported two cases of pernicious anaemia in which the initial high figures of serum iron fell to a low level during a remission. The following is a study of the variations of serum iron before and after treatment in the macrocytic anaemias. It was thought that a definite correlation between an early fall in serum iron and effective therapy might provide a quick and simple method of assessing the effect of a haematinic in the macrocytic anaemias.

Material and Methods

Macrocytic anaemias of all types, such as pernicious anaemia, the sprue syndrome, liver disease, and pregnancy, were studied. The patients were treated by an injection of a haematinic, usually vitamin B_{12} or folic acid, in hospital. The response in the blood was measured by the rise in erythrocytes after 15 days (Ungley, 1949) and by the reticulocyte count.

The blood for serum iron estimation was always taken at about 10 a.m. to avoid errors due to the diurnal variation (Vahlquist, 1941 ; Hoyer, 1944 ; Hamilton *et al.*, 1950). Modern methods for serum iron determination (Laurell, 1947 ; Vannotti and Delachaux, 1949) are simple and accurate. A fastidious cleanliness is needed, as iron is a common contaminant ; so that all-glass syringes and specimen tubes, dry sterilized and specifically cleaned, are used for taking samples of blood. The following technique, adapted by P. W. Perryman (1948, personal communication), has been used.

In a centrifuge tube is placed 4 ml. of serum, to which 1 ml. of 6 N HCl is added, mixed well, and left to stand for ten minutes. Then 3 ml. of 20% trichloracetic acid is added, stirred with a glass rod, left for 5 minutes, and centrifuged at high speed for approximately 20 minutes. (A longer period may be necessary if particles are still present when the supernatant fluid is drawn off.) Then 4 ml. of supernatant fluid is placed in a glass-stoppered tube and approximately 50 mg. of ascorbic acid added and the solution left for 10 minutes, with occasional shaking to encourage the ascorbic acid to dissolve. Finally, 0.5 ml. of $\alpha\alpha$-dipyridyl in 0.1 N HCl, or 1 ml. of 0.1% orthophenanthroline, and 0.5 ml. of concentrated ammonia solution, are added. The tubes must be agitated well immediately on adding these last two solutions. 1 ml. of doubly distilled water is added to bring the final solution to 6 ml. for the cell of the spectrophotometer (Unicam, S.P.500). The blank consists of 3 ml. of doubly distilled water, 0.5 ml. of 6 N HCl, 1.5 ml. of 20% trichloracetic acid, then ascorbic acid, reagent, and ammonia solution as above.

Calibration curves were prepared by making known solutions of ferrous ammonium sulphate, through the range of 50 to 500 μg. per 100 ml., and putting them through the same process as for serum. If, for other reasons, it is desirable to avoid using strong ammonia in the laboratory,

0.5 ml. of saturated sodium acetate can be used as a buffer instead; for this, the serum is incubated at 37° C. for one hour with 2 ml. of 0.3 N HCl, then 2 ml. of 20% trichloracetic acid is added, and the solution left for one hour. Otherwise there is no change in the technique. All the glassware is washed, left in cleaning fluid (potassium dichromate 100 g., sulphuric acid conc. 800 ml., water 1,200 ml.), washed thoroughly again in running tap-water, then rinsed in distilled water. All the reagents must be chemically pure, and made in doubly distilled water.

The standard deviation of a single determination from the mean, calculated from 42 duplicate analyses, was ±3.05 μg. per 100 ml. of serum. Seventy-four samples were analysed from 48 normal males and 26 normal females. The mean serum iron concentration was 126.8 μg per 100 ml. (S.D. 30), and the values ranged from 71 to 205 μg. per 100 ml. The mean serum iron for males was 130.8 μg. per 100 ml. (S.D. 30.8); for females, 119.4 μg. per 100 ml. (S.D. 27).

Results

The serum iron was studied before and after therapy on 100 occasions. In 60 the treatment was effective, and in every case the serum iron fell to a low figure during the remission. In 40 the haematinic was ineffective and the serum iron remained within similar limits. The fall in serum iron after successful treatment is striking and abrupt (Fig. 1). It was next determined how soon this took place,

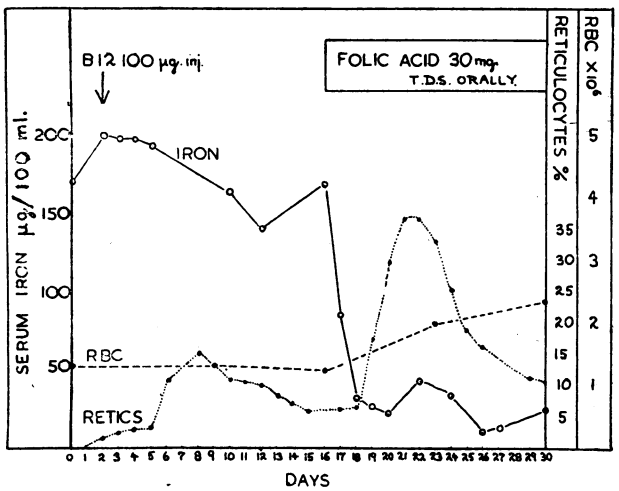

FIG. 1.—The fall in serum iron after effective treatment by folic acid in a case of megaloblastic anaemia of unknown origin.

and the earliest reliable time to estimate this change. To six patients with pernicious anaemia an injection of 100 μg. of vitamin B_{12} was given, and readings were taken at two-hourly intervals for eight hours; a significant fall occurred in one only. However, at 24 hours a significant change was obvious in 21 out of 23 cases; in the two with little or no change a further figure at 48 hours showed the characteristic fall. It was thereafter decided to rely upon the 48-hour reading of the serum iron.

The 48-hour reading of the serum iron has been studied on 33 occasions, and the change correlated with the result of therapy in every instance except one, a case of steatorrhoea in which a submaximal reticulocyte response occurred after vitamin B_{12} without any rise in the red blood cells. Here the fall was transient and returned to normal within the week. The maximum change was 228 μg per 100 ml. (from 278 to 50 μg. per 100 ml.), and the minimum significant fall was 20 μg. per 100 ml. (from 46 to 26 μg. per 100 ml.); the mean was 105 μg. per 100 ml. Whatever the initial height of serum iron, the values tended to fall to about the same level (Fig. 2); they then remained at about 50–60 μg. per 100 ml.—unaffected by the reticulocyte response—until the blood count returned to normal. Insufficient dosage of the haematinic was shown by the serum iron rising to the previous levels. Impending iron deficiency was indicated by a fall to a lower level; values below 40 μg. per 100 ml. were suggestive, and below 30 μg. per 100 ml. diagnostic of this. The mean of nine cases at one week that later developed iron deficiency was 27.3 μg. per 100 ml. (range from 11 to 39 μg. per 100 ml.). This often preceded the signs of iron deficiency in the blood count by several weeks.

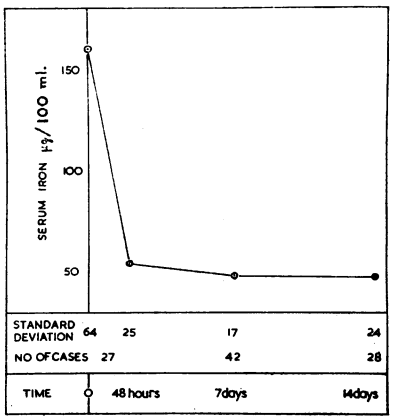

FIG. 2.—A composite graph showing the fall in serum iron following effective therapy in cases of macrocytic anaemia.

The total iron-binding capacity (Cartwright and Wintrobe, 1949) was measured on five occasions before and after successful therapy. There is no significant change unless iron deficiency develops, when the typical high figures are seen. Twelve normal controls were given injections of vitamin B_{12} or folic acid, and no change took place in the serum iron or total iron-binding capacity.

Discussion

The 48-hours serum iron test is a reliable method of assessing the effect of haematinics in the macrocytic anaemias. A fall in the serum iron is probably the earliest sign of a haematological response, for the bone-marrow reversion is not complete until 32 to 72 hours (Davidson *et al.*, 1942), and the reticulocyte response does not appear for several days. The test is useful if the level of the initial red-cell count is such (3,000,000 cells per c.mm. or more) that the reticulocyte change is slight or inconclusive, and in out-patient trials where the patient cannot attend daily for reticulocyte counts. It is helpful in severely ill patients, in whom the earliest indication of effective therapy is needed, as waiting may be dangerous. It is probably unaffected by a blood transfusion being given at the same time as the haematinic. It is the first sign of impending iron deficiency. It is not necessarily suggested that this test should be used for routine clinical work, as the reticulocyte response and the rise in red cells are already sufficient. However, the study of the macrocytic anaemias and their response to various haematinics is becoming a complex problem, and it may be that a simple test, with a precise and sharp end-point, will be of value.

The explanation of the fall to a low level is perhaps that the rate of release of iron from the stores, possibly by enzymic action, cannot keep pace with the increased demand. It is interesting that, irrespective of the initial height, the level after successful therapy is similar in all. This figure may represent a state of physiological balance between the stores and the bone marrow. The test is an index of an increased turnover of iron in the body, and the low serum iron a measure of erythropoietic activity.

Summary

A test for assessing the effect of haematinics in the macrocytic anaemias is described.

The fall in the serum iron is the first sign of effective therapy.

The level of the serum iron gives the earliest indication of impending iron deficiency.

I am grateful to our deputy biochemist, Mrs. R. M. Lainchbury, for doing the serum iron estimations, and to my colleagues

on the staff of the United Birmingham Hospitals for allowing me access to their cases. Dr. J. A. H. Waterhouse, of the department of medical statistics, also gave me helpful advice.

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IRON DEFICIENCY IN PREGNANCY

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Some fall in the level of haemoglobin during pregnancy is usual. This relative anaemia is often attributed to the rise in blood volume of 18–23% (Dieckmann and Wegner, 1934; Roscoe and Donaldson, 1946; Berlin *et al.*, 1953) which occurs towards the end of pregnancy. Since the haemoglobin levels of most non-pregnant women range from 80 to 95%, levels of haemoglobin of 70–85% at the end of pregnancy have come to be accepted as normal.

The fact that throws doubt on the "physiological" nature of the anaemia of pregnancy is that the anaemia can in most cases be prevented by the administration of iron (Corrigan and Strauss, 1936; Fullerton, 1936; Wills *et al.*, 1947; Klopper and Ventura, 1951; Scott and Govan, 1949; Benstead and Theobald, 1952; Davis and Jennison, 1954).

The present investigation does little more than confirm this finding, but it was thought that our evidence should be added to that already available both because low haemoglobin levels in pregnancy are undesirable and because there is a continuing failure to recognize that they are unnecessary.

Plan of the Present Investigation

The investigation was carried out on patients booked for domiciliary delivery and attending two local health authority antenatal clinics between January, 1951, and April, 1953. All patients presenting themselves before the end of the fourth month of pregnancy were included. The haemoglobin levels were measured by the M.R.C. neutral grey photometer, taking 100% haemoglobin to be equivalent to 14.8 g.% of haemoglobin. Haemoglobin estimations were made at the first attendance, at 28 weeks, at 38 weeks, and six weeks after delivery. These dates are approximate, and occasionally the post-natal reading was at a rather later date.

Every patient was given an iron preparation by mouth from the time of first attendance until delivery. This was given in the form of one "fersolate" tablet (containing 3 gr. (0.2 g.) of ferrous sulphate) three times a day. The preparation was changed to "ferro-redoxon" (containing 2.04 gr. (132 mg.) ferrous sulphate and 50 mg. of ascorbic acid) if the patient complained of digestive disturbances or if the haemoglobin level had not risen. This change was made in about half the cases, and it appeared that the preparation containing ascorbic acid was better tolerated. The main difficulty in satisfactory iron therapy during pregnancy is that patients who feel well cannot be relied on to take it regularly, partly because any minor discomfort is attributed to it and partly because they see no necessity for it. We explained that taking iron regularly would make them feel "fighting fit" for their labour and also for their return to household duties after the lying-in period. In general this produced ready co-operation. At every attendance the patient was given the exact number of tablets to cover the period till she was due to come again and was asked to bring back the box with any that were left. These were counted and the number was recorded. It is clearly impossible to be certain that all the tablets not returned were consumed, but we felt that the record was as accurate as it could be, short of seeing the tablets swallowed.

The investigation included 138 patients. Of these, five could not be persuaded to persevere with iron and were excluded. In 26 instances the complete set of haemoglobin estimations was not obtained, either because the baby arrived before the calculated date, so that the 38-week reading was not made, or because the patient removed from the district or was transferred to the care of a hospital or general practitioner. Three further patients were excluded because they were given blood transfusions after post-partum haemorrhage. The 104 remaining cases are listed according to age and parity in Table I. There were no complications of pregnancy or labour in these patients apart from three forceps deliveries.

TABLE I.—*Age and Parity of* 104 *Women who Took Iron Regularly During Pregnancy*

Age	Parity					
	0	1	2	3	4	5
Under 20 ..	3	—	—	—	—	—
20–29	14	18	11	6	1	—
30–39	1	9	12	17	6	1
40 or over ..	—	—	3	1	1	—
Totals . ..	18	27	26	24	8	1

Results

A difficulty in the analysis of the results of this survey is that a few patients failed to respond to iron therapy. We have isolated as a separate group all those in whom the haemoglobin level was still below 85% at 38 weeks and have termed them "non-responders." Table II shows the distribution of haemoglobin levels before the end of the fourth month of pregnancy in both "responders" and "non-responders" and indicates that there is no systematic difference in this respect between the two groups.

TABLE II.—*Haemoglobin Levels Before the End of the Fourth Month of Pregnancy in* 104 *Patients who Took Iron Regularly*

	Hb Levels				Total
	80% or Less	81–89%	90–99%	100%+	
Responders ..	15	33	33	11	92
Non-responders	4	3	5	0	12

Note.—Statistical examination of the age and parity of the responders does not show any significant difference between the four groups.

The effect of iron on the haemoglobin level is illustrated in the chart, where the "responders" have been subdivided according to their initial haemoglobin. This shows that when the initial haemoglobin is below 90% the administration of iron leads to a marked rise during pregnancy. When the initial haemoglobin is above 90% there is little systematic change in the level. In all the "responding" groups the haemoglobin level is around 98% at 38 weeks and remains at much the same level for six or more weeks after delivery. The "non-responders," who show a general downward trend