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According to a British United Press report from Frankfurt, 428 surgeons, 125 dentists, and 30 veterinary surgeons fled from Eastern Germany to the West in the first eight months of this year.

TREATMENT OF IRON DEFICIENCY WITH FERROUS FUMARATE

ASSESSMENT BY A STATISTICALLY ACCURATE METHOD

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It is desirable to know how the new iron preparation ferrous fumarate compares with pre-existing therapies. To commend itself for routine use it should be at least as effective as established drugs, and have fewer or no unpleasant side-effects, as well as being safe. The results reported below show that these requirements appear to be satisfied by ferrous fumarate.

For many years the mainstay of iron therapy has been ferrous sulphate. In 1836, Ashwell, when discussing the treatment of chlorosis, said that the sulphate of iron was "probably the most efficacious and possessed more specific properties than any of the rest." Davidson (1933) urged the use of ferrous sulphate tablets, adequate treatment with which still costs only one penny a week. Gastric symptoms such as epigastric discomfort, nausea, and vomiting have often been reported after its use. In a recent comparative trial the incidence of such side-effects was found to be 13% with ferrous sulphate (O'Sullivan, Higgins, and Wilkinson, 1955). Girdwood (1952) drew attention to a strong psychological intolerance shown by his patients towards tablets of ferrous sulphate, but only when they were coated green. Kerr and Davidson (1958) showed by a double blind trial, however, that unrecognized control pills caused the same incidence of side-effects as did the active iron pills, including ferrous sulphate. Ingestion of an overdose of ferrous sulphate by children who have mistaken the green sugar-coated tablets for sweets has resulted in death (Forbes, 1947; Thomson, 1947) and has been shown to cause pyloric stenosis and fibrous stricture of the pyloric antrum or mid-portion of the stomach (Ross, 1953; Shepherd, 1955). Despite these disadvantages, ferrous sulphate is still accepted as a very effective therapeutic compound.

Many alternative potent preparations of iron have been used in order to avoid undesirable side-effects and dangers to children. Ferrous gluconate, originally recommended by Reznikoff and Goebel (1937), has lately become one of the most popular of iron tablets. These tablets are sugar-coated and relatively cheap, although four times as expensive as ferrous sulphate. The incidence of toxic side-effects has been estimated at 4%, with clinical efficacy similar to that of ferrous sulphate (O'Sullivan *et al.*, 1955). Deaths attributable to overdosage had not been reported by 1955 (Hoppe, Marcelli, and Tainter) and no report of a death resulting from ferrous gluconate has been seen since then. There have been many other effective but even more expensive

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iron preparations on the market. It has yet to be proved that they are better than the established drugs.

Ferrous fumarate, an organic iron compound, is a new contestant in the field. It is dispensed as small light-brown 200-mg. tablets which do not resemble sweets. The iron contained in them is very stable, thus removing the need for sugar coating, and this permits rapid disintegration of the tablets when ingested. If a tablet of ferrous fumarate is sucked it leaves a very slightly unpleasant taste which classes it apart from sweets, but there is no metallic astringent sensation.

The accompanying Table shows the ferrous iron content of four salts and the standard tablets prepared from them, together with their relative costs. The prices quoted have been taken from price-lists supplied in autumn, 1958.

Iron Content and Costs of Four Iron Preparations

	Ferrous Iron (Approx. %)	Standard Tablet (mg.)	Ferrous Iron per Tablet, Approx. (mg.)	Cost of Treatment for One Week (21 Tablets) at Hospital Rates per 1,000 Tablets
Ferrous fumarate	33	200	65	5d.*
gluconate B.P.	12	300	37.5	4d.
Ferrous succinate	25	150	37.5	4½d.*
Exsiccated ferrous sulphate B.P.	30	200	60	1d.

* Exclusive of purchase tax 1½d.

The toxic effects of ferrous fumarate on laboratory animals have been studied by Berenbaum, Child, Davis, Sharpe, Tomich, and Chalmers (1959). Rabbits given large doses of ferrous sulphate tablets developed severe gastric necrosis and chemical hepatitis. Ferrous gluconate produced similar but less intense effects, whereas ferrous succinate and ferrous fumarate usually caused little or no inflammatory reaction. In cats, the dose of ferrous fumarate required to produce vomiting was three times greater than the equivalent doses of the other three iron preparations.

It is the purpose of this paper to describe the effects of giving ferrous fumarate tablets to 64 patients suffering from iron deficiency, and to measure, so far as is possible, the efficacy of the drug and its toxic effects in clinical use.

Material and Methods

Since June, 1957, 64 patients have been treated with ferrous fumarate, 200 mg. (one tablet), by mouth three times daily after food. Fifty-five of these patients were selected as the result of peripheral blood examinations made in the departments of haematology of the Royal Infirmary and the Royal Hospital, Sheffield, at the request of hospital consultants and family doctors. Where a blood examination showed anaemia of any degree with definite red-cell hypochromia and it was believed that the anaemia was of iron-deficiency type, permission was sought from the clinician in charge of the case to treat the patient. The study was deliberately not restricted to the 37 patients who had a simple iron-deficiency anaemia unassociated with blood loss and resulting from too little dietary iron. It included 18 others suffering from "complicated" iron deficiency, some having heavy menstrual loss or alimentary blood loss, the remainder having various diagnoses such as are found in any medical or surgical ward, the patients being unselected apart from the presence of iron deficiency. The initial mean corpuscular haemoglobin

concentration (M.C.H.C.) was estimated in 46 of these patients and was below 32% in all (normal range 32–36%). No patient in the main group had received iron therapy during the preceding six months.

Capillary blood was examined at weekly or fortnightly intervals over eight weeks during treatment. The haemoglobin estimations were made as oxyhaemoglobin, using the M.R.C. grey wedge photometer and the films stained with Leishman's stain. Where the M.C.H.C. was estimated, venous blood was used. The patients were given the opportunity of discussing symptoms at each visit, although leading questions were reserved for the final visit. No patient having once been treated with ferrous fumarate has been excluded from this series on the grounds of failure to respond or toxic effects.

Six women, one of them pregnant and all of them iron-deficient, were given ferrous fumarate as a severe test of its freedom from side-effects, because they had proved themselves to be intolerant to all the other iron preparations they had been given. Four patients suffering from post-gastrectomy iron-deficiency anaemia are discussed as a separate group.

Results

In the main group of 55 patients, the haemoglobin levels of the first 47 on treatment have been analysed statistically. The records for the remainder became available after this had been carried out, but the figures are consistent in every way with those included in the analysis.

Two pieces of statistical analysis were carried out on these data, and are reported here. The aim of the first of these was to study the mode of return of the haemoglobin levels to normal under treatment so as to obtain a rational criterion of success. The second has been concerned with the evaluation of the trial of ferrous fumarate in terms of this criterion, obtaining a figure of known statistical accuracy with which other workers may compare their own results using ferrous fumarate or any other iron preparation.

Analysis 1

In Fig. 1 is shown an example of the relationship between the haemoglobin level after a fixed number (k) of weeks on therapy and the initial haemoglobin level (in Fig. 1, $k=2$).

FIG. 1.—Haemoglobin percentage after two weeks of therapy related to initial haemoglobin.

Each point plotted corresponds to a particular patient, the total number of points being fewer than 47 because some patients did not appear for examination at the end of the appropriate week. A line of regression has been fitted, and may be taken as giving the relationship between the mean haemoglobin after k weeks and the initial haemoglobin. The two symbols used for the plotted points are for the different categories of patient, simple iron deficiencies being kept distinct from the complicated cases. There was no evidence (either *prima facie* or revealed by statistical significance tests) of any differences in the relationship for these two categories. A similar analysis was carried out for each week in therapy up to the eighth—that is, $k=1$ to 8—and it was observed that the regression line became higher and flatter as time went on, indicating the gradual return to normality. After a critical statistical examination of these trends it was found to be justifiable to summarize the return of haemoglobin to normal by means of a family of curves, shown in Fig. 2, which show the mean pattern of return to normal for patients starting treatment from different levels of haemoglobin.

Fig. 2 demonstrates clearly how markedly the effect of initial differences in haemoglobin level influences the rate of response during the first few weeks of therapy, the more anaemic groups responding more rapidly. The difference between the groups lessens with time and effectively dies out by the seventh week. The observations suggest that the haemoglobin level is still climbing slightly at the end of the eighth week, but it

FIG. 2.—Mean haemoglobin percentage at successive stages of therapy for different initial haemoglobin levels. (100% Hb = 14.8 g./100 ml.).

FIG. 3.—Recovery attained at successive weeks, expressed as percentage of increase of Hb achieved by eight weeks.

seems unlikely that any serious error will be committed by accepting the eight-week figure as effectively normal. Observations of the haemoglobin levels of individual patients deviate randomly from the appropriate value given by Fig. 2, with a standard deviation of 6.6.

The pattern of return to normal does in fact admit a more concise representation than Fig. 2. If each of the curves of Fig. 2 is re-scaled so as to increase from 0 initially to 100 at eight weeks, the result is the single curve, applicable to all initial haemoglobin levels, shown in Fig. 3.

That all curves re-scale *exactly* into this curve is of course a consequence of the statistical method of fitting, but an alternative method of fitting which is described in the statistical appendix and which does not beg this important question leads to curves which differ only very slightly and do not give a superior fit to the data.

Analysis 2

In the light of Analysis 1, it was decided to summarize the effect of treatment on the haemoglobin level of individual patients by expressing, as a percentage, the ratio of the correction achieved by the end of the third week to that achieved by the end of the eighth week ;

$$p \equiv \frac{x_3 - x_0}{x_8 - x_0} \times 100$$

where x_0 symbolizes the initial haemoglobin value, and x_3 and x_8 the measurements at the end of the third and eighth weeks of treatment respectively (see Statistical Appendix).

For the 53 available cases, the mean value of p —that is, the mean percentage recovery achieved by the end of the third week—was 59.0% ; the standard deviation of p was 17.3, implying a variation from this figure of as much as ± 34.6 for individual cases, and implying a statistical accuracy for the mean of ± 4.8 (based on an estimated standard error of 2.4).

Response of Particular Patients to Ferrous Fumarate

1. Side-effects Caused by Ferrous Fumarate

Although each patient was repeatedly given the opportunity of commenting on the tablets, only 2 of the 55 patients in the main series made any adverse comment, remarking on slight epigastric discomfort which began 10 minutes after taking the tablets and lasted about two hours. Such discomfort was felt only during the first 10 days of therapy and disappeared entirely during continued treatment. Five patients considered constipation to be attributable to the tablets.

Amongst the nine others treated with ferrous fumarate but not as part of the main series, one suffered undesirable side-effects. She had been given ferrous fumarate because of her intolerance of other iron preparations, and is described in subsections 2 and 3 below.

2. Patients Intolerant of Other Iron Preparations

Two of the patients in the main series who remained symptom-free when taking ferrous fumarate had customarily felt sick with ferrous gluconate, and a third had vomited with ferrous sulphate. Outside the main series, six women were given ferrous fumarate on account of their intolerance of other iron preparations.

The *first*, aged 47, with simple iron deficiency, was becoming more anaemic in spite of two or three drops of colloidal iron which she took with food three times a day.

Even such small amounts caused slight nausea, but ferrous sulphate and ferrous gluconate caused vomiting and could not be tolerated at all. The *second*, aged 32, had been able to take an expensive chelated iron preparation during pregnancy, but not ferrous sulphate or ferrous gluconate. The *third*, aged 38, with menorrhagia, had been so intolerant of ferrous sulphate and ferrous gluconate by mouth that she had required two courses of intravenous iron in recent years. The *fourth*, a nurse aged 20, who was only slightly anaemic, had developed diarrhoea whenever she took ferrous gluconate. The *fifth*, aged 55, who suffered from hereditary haemorrhagic telangiectasia with some blood loss, had felt epigastric discomfort and anorexia whenever she took a colloidal iron preparation. These patients took ferrous fumarate with benefit and without side-effects. The *sixth* patient, while intolerant of four other iron preparations, was also intolerant of ferrous fumarate, and is described below because, in addition, she failed to respond to it.

3. Failure to Respond to Ferrous Fumarate

Alone of all the patients given ferrous fumarate one woman made no response whatsoever during the fortnight she was treated. She was aged 54, and since the age of 18 had received 12 blood transfusions and four courses of parenteral iron, which had helped her greatly. She had taken iron many times before, and iron by mouth had never helped her but had often made her sick. When given ferrous fumarate as a trial of its side-effects, her haemoglobin was 9.3 g./100 ml. (63%) and the red cells were microcytic and hypochromic. She took ferrous fumarate three times daily, but felt nauseated much of the time and vomited within two hours of taking most tablets. This nausea and vomiting continued until the tablets had to be stopped at the end of two weeks, the haemoglobin remaining at 9.3 g./100 ml. and the film showing no evidence of an influx of normochromic cells. She persisted with treatment for as long as she did because of her apparently genuine desire to co-operate. The haemoglobin responded well to a subsequent course of iron dextran given intramuscularly, rising to 13.6 g./100 ml.

4. Post-gastrectomy Iron Deficiency

The responses were followed of four patients on whom partial gastrectomy had been performed for peptic ulceration some years previously and who had developed iron-deficiency anaemia.

The first two patients, whose operations had been 8 and 10 years previously, responded well to ferrous fumarate and achieved normal and apparently maximum haemoglobin levels within eight weeks. The third patient whose operation had been seven years previously, responded very slowly, his haemoglobin level being 8.9 g./100 ml. at the start of therapy, rising to 12.3 g./100 ml. at eight weeks. Not until 13 weeks did it reach its top level of 15.4 g./100 ml. Examination of the stools of this patient was consistently positive for occult blood, but the source of the bleeding could not be identified without further surgery.

The fourth patient, whose partial gastrectomy had been four years previously had been taking colloidal iron medicine for two and a half years without clinical benefit and presented with a haemoglobin of 8.0 g./100 ml. and an M.C.H.C. of 26.8%. She did respond slowly to ferrous fumarate, but after five weeks her haemoglobin had risen to only 8.7 g./100 ml. Further investigations were therefore performed. These included a radio-iron absorption test, carried out after all other iron therapy had been stopped for one week. 0.66 g. of ferrous glycine sulphate labelled with ^{59}Fe (117 mg. of elemental iron) was taken by the patient, and all stools were collected until they

contained no more significant radioactivity. The faecal recovery was 49% of the ingested dose of radio-iron. When the radio-iron absorption test was completed she was given 100 mg. of elemental iron in the form of ferrous fumarate. One and a half tablets of this were mixed with water, in which they formed a suspension in a matter of seconds, and this was taken fasting. The serum iron was estimated before and again two hours after this dose and was found to have risen from 20 to 102 $\mu\text{g.}/100\text{ ml.}$ Stool examination for occult blood was positive at this time. Treatment was then resumed with ferrous fumarate, and the haemoglobin continued to rise slowly.

5. Histamine-fast Achlorhydria

Only two patients are known to have a histamine-fast achlorhydria. They responded as satisfactorily as the others.

Discussion

It is of interest that the response to ferrous fumarate was as good for the group of "complicated" iron deficiencies as for the uncomplicated group, all the patients being unselected initially so long as they were anaemic and showed red-cell hypochromia. It is obvious, nevertheless, that there will be a limit to the amount of current blood loss or "toxic" influence which can be borne by a patient without it depressing the response to iron therapy.

Although no controls have been provided with this series, the results have been presented in a way which should allow of comparison with other series of patients treated with iron compounds who have been followed by the percentage rise of haemoglobin in the peripheral blood. Such estimations—for example, those shown in Fig. 2—do not necessarily reflect accurately the whole haemoglobin production of the bone marrow, as was well shown by Whitby (1949), who demonstrated that considerable adjustments are made to the total circulating haemoglobin which are not reflected by the percentage haemoglobin levels of the peripheral blood. Fig. 2, however, allows one to estimate the expected rise of haemoglobin percentage in a patient about to start ferrous fumarate therapy.

The response to ferrous fumarate has not been summarized in terms of percentage rise of haemoglobin per day. If Fig. 2 is studied it can be seen that the average rise in haemoglobin per day for the same group of patients can be made great or small according to the number of weeks over which the average is taken. Another important variable is the rise in haemoglobin per day in the severely anaemic patients, which is greater than in the less affected. Such variables make it difficult to describe the results of a clinical trial of iron therapy by a simple figure, applicable to all cases, in terms of haemoglobin rise per day. This adds to the difficulty of comparing quantitatively the results obtained by different workers. The method of presentation used here can be applied without modification to any similar series provided that the haemoglobin level has risen to near maximum by eight weeks. An iron preparation which does not achieve this condemns itself *ipso facto*.

The simplest comprehensive description of the response of the haemoglobin level to the drug is the curve given in Fig. 3, and the existence of such a curve is of considerable interest. Such a single curve has provided a rational basis for summarizing the results of the present trial. Thus the mean percentage of the return to "normal"—that is, the eighth-week value—achieved at any stage of therapy may be read off the

curve at once, without regard to the initial haemoglobin. For example, about the 18th day of treatment the haemoglobin levels of all groups of patients had returned exactly halfway to normal. It has not yet been shown that the result of therapy with other forms of oral iron can be characterized by a single curve, but there is no reason apparent why this should not be possible.

Having fitted a single curve to depict the therapeutic response of a series of cases, it is still a difficult matter statistically to measure the differences between two or more such curves. Accordingly the mean proportionate return to normal of a group of patients after three weeks ("p" in Analysis 2) has been recommended as an appropriate and simple measure of success, suitable for assessing the results of such a trial as this. It is based on the potential existence of the common curve, but does not demand its construction, and requires only three haemoglobin readings in all, on each patient, but the timing of these must be uniform. The end of the third week was chosen arbitrarily as being a convenient time near the halfway figure.

Fig. 3 draws attention to the fact that mild anaemias appear to need as prolonged therapy as the more severe anaemias. This fact may be explained in part by the way in which the amount of iron absorbed from the gut is proportional to the degree of erythropoiesis in the bone marrow as shown by Bothwell, Pirzio-Biroli, and Finch (1958). These workers also showed that depletion of iron stores is associated with an increased absorption of iron from the gut. Unlike erythropoiesis, this influence should be uniform in the patients of the main series here, who can all be presumed to have had depleted iron stores. Anaemia *per se* does not appear to be a controlling factor in iron absorption (Pirzio-Biroli, Bothwell, and Finch, 1958). Although the haemoglobin levels were effectively normal by the eighth week (Fig. 2), the fact that they were still climbing slightly would suggest that more prolonged therapy is indicated. We consider, for routine treatment, that a three-months course of iron therapy by mouth is the minimum for any iron-deficient patient regardless of the initial haemoglobin level. This recommendation is directed towards the treatment of the anaemia and takes no account of the need for building up iron reserves.

There is a point of interest in the close similarity between the curves in Fig. 2 and those in Chart 2 of the publication by Isaacs, Bethell, Riddle, and Friedman (1938), where the curves represent the average rate of formation of red cells in patients with pernicious anaemia after treatment with intramuscular liver extract. These authors point out that a red blood cell count of 5,000,000/c.mm. may be expected at the end of eight weeks, regardless of the initial count. Although iron and vitamin B₁₂ seem to have such different points of action it appears that there may be some governing factor which is common to both and determines this common pattern of response.

Patients who are iron-deficient after partial gastrectomy usually respond satisfactorily to iron therapy by mouth (Baird, Blackburn, and Wilson, 1959), and this was shown in the present series by two patients whose rise in haemoglobin corresponded to the figures represented in Fig. 2. There were two examples of a slow response related, at least in part, to alimentary

blood loss. Ferrous fumarate was slowly effective therapeutically in both these patients, one of whom had failed to respond at all to a colloidal iron preparation. This patient absorbed radio-iron well and showed evidence of a satisfactory absorption of iron given as ferrous fumarate, despite her slow clinical response. Baird *et al.* (1959) have shown in 38 patients who were suffering from post-gastrectomy iron-deficient anaemia that prolonged treatment with iron (mean time 6.5 months) was often required even in the absence of alimentary bleeding.

Only one patient among the 64 treated failed to respond at all to ferrous fumarate. This patient appears to be suffering from iron malabsorption, although this has not yet been proved. The cause of the apparent malabsorption was not known at the time of the trial, but the patient had been treated successfully for lupus vulgaris seven years before. The gastric irritation caused by the tablets seemed genuine.

Only two patients in the series are known to have a histamine-fast achlorhydria. Since they responded to ferrous fumarate as promptly as the others it would suggest that hydrochloric acid is not essential to the absorption of the iron from ferrous fumarate any more than it is for ferrous ammonium sulphate (Grace, Doig, and Wolff, 1954), or for iron incorporated into the chemical structure of foodstuffs (Moore, 1955). This *in vivo* observation is of interest, since tablets of ferrous fumarate are more soluble *in vitro* in dilute hydrochloric acid than they are in water.

The incidence of toxicity and side-reactions over the whole group of 64 patients treated was low. Only the patient just referred to who had presumptive malabsorption of iron had nausea and vomited, and it seems debatable whether the toxic response of such a person is used justifiably as a criticism of a drug which is so conspicuously free from troublesome side-effects in all the patients who did respond. Only 2 out of the remaining 63 patients reported mild epigastric discomfort for the first 10 days on treatment.

It would seem that ferrous fumarate tablets, which disintegrate so rapidly in the mouth, may thereby make a material contribution to the treatment of those patients who cannot swallow tablets and who have formerly had to take liquid iron preparations or receive iron parenterally. In addition it makes available an iron preparation which has a very low incidence of gastro-intestinal side-effects, which, when present, are mild.

Summary

All of 55 patients suffering from untreated iron-deficiency anaemia and forming the main series in this investigation responded well to ferrous fumarate, 200 mg. (one tablet) three times daily. Nine other patients were given ferrous fumarate for reasons described.

Of the 63 patients who responded to ferrous fumarate, 2 (3%) complained of mild epigastric discomfort for 10 days. The remaining patient, who did not respond and who had presumptive iron malabsorption, had more marked gastric symptoms. Eight patients giving a history of alimentary disorder when taking other iron preparations accepted ferrous fumarate without a symptom. Four patients suffering from post-gastrectomy iron-deficiency anaemia are described separately. Two of them responded very slowly to treatment.

The haemoglobin figures in the main series have been subjected to two analyses. The first shows that the responses to therapy of all the patients can be expressed by a common curve without regard to the degree of the initial anaemia. The existence of this curve establishes the importance of continuing iron therapy for as long a time in mild anaemia as in severe cases and demonstrates that this should be for more than two months.

The second analysis is based on the establishment of this common curve. The mean percentage recovery attained by the end of the third week was 59%, with a statistical accuracy for the mean of ± 4.8 . It is suggested that this method of analysis and presentation of data with known statistical accuracy will allow of comparisons between trials of different iron preparations. The haemoglobin levels at the start of therapy, after three weeks, and on reaching normal are required for this method of analysis.

The willingness with which patients were referred for treatment by the consultants of the hospitals concerned, by their staffs, and by family doctors, is gratefully acknowledged. Dr. E. K. Blackburn, in whose department the work has been carried out, has been particularly helpful at all stages. Dr. I. McLean Baird kindly performed the radio-iron study in one case. Thanks are also due to Mr. J. Monaghan and Miss Joan Ripley for technical help; to Mr. A. Howard; to the Board of Governors of the United Sheffield Hospitals for a research grant; and to Mrs. W. M. Wright and Miss D. Kirk for computational assistance. Glaxo Laboratories Ltd. kindly supplied tablets for the trial and have assisted in other ways.

Statistical Appendix

Analysis 1

Lines of regression of haemoglobin at the week (k) on initial haemoglobin were fitted for k=1 to 8 inclusive and for the two categories of patient (simple and complicated iron deficiency) and the standard errors of their coefficients were estimated. Differences between slope and differences between positions of the lines for the two categories of patient were compared with their standard errors, and in no case proved statistically significant at the 5% level, therefore a single regression was computed for each week, the categories being combined. The regressions for the different weeks were of course subject to sampling errors, which were largest for k=5 and 7, for which only a few records were available.

The method of analysis first adopted was to fit curves of suitable exponential type to the slopes of the regression lines; and to their heights at 59.

Curves were fitted by weighted least squares (weights being inversely proportional to sampling variances) and provided approximate χ^2 criteria of goodness of fit of 2.27 and 11.69 respectively, each with six degrees of freedom. The failure of these to attain the 5% level of significance, along with the apparent lack of trend in the deviations from the fitted curves, confirmed the adequacy of these curves as a summary of the data, and curves of the form shown in Fig. 2 were deduced from them. However, it was noted that when these were re-scaled, as in Fig. 3, they became almost identical, and it was therefore decided to fit curves to slope and height which were related in such a way as to give a single curve as shown in Fig. 3. This was done by an approximation to least squares. The corresponding joint χ^2 criterion was 9.83, with 13 degrees of freedom, indicating a fit which was not only satisfactory but better than before. This seems paradoxical until it is remembered that the new curve fitted to heights comes from a more complicated mathematical family than appeared to be necessary for the first analysis, and is thus more flexible.

Evidently there are adequate grounds for summarizing the data by the curve of Fig. 3.

Analysis 2

The three observations required for computing p were available in 27 cases. In 26 of the remainder, either x_3 or x_8 was not available, and the following expedients were adopted as necessary: (1) x_3 interpolated between observed values—for example, $\frac{1}{2}(x_2 + x_4)$, or $\frac{2}{3}x_2 + \frac{1}{3}x_5$ —a procedure justified by the approximate straightness of the curves of Fig. 2 over the range one to six weeks. (2) x_7 used in place of x_8 , with a slight adjustment, using the appropriate curve of Fig. 2. (3) x_8 estimated entirely from the appropriate curve of Fig. 2.

In two cases the data were insufficient for the application of these expedients, and were therefore not used.

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PARTIAL THORACIC STOMACH IN CHILDHOOD

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The condition known as congenital short oesophagus, hiatus hernia, or partial thoracic stomach has interested paediatricians and surgeons only comparatively recently. It is clear from the work of Carré *et al.* (1952) that the course is generally benign, symptoms subsiding after the first year or two of life in the majority of children, though it seems probable that they may recur in adult life. Unfortunately, not all cases pursue this favourable course, and vomiting may continue intermittently for years. Stricture formation is the main complication to be feared, but as yet there is no evidence to show that prompt treatment reduces the incidence of this complication or whether it may be predicted. The part that surgery has to play in management is still undecided. The purpose of this paper is to present an analysis of the cases of partial thoracic stomach attending the Hospital for Sick Children, Great Ormond Street, over a period of 10 years. Most of these cases were included in an interim report by Waterston (1954).

Material

During the 10 years 1945 to 1955 137 children attending the hospital were diagnosed as having partial