IRON-DEFICIENCY ANAEMIA IN CHILDREN:
Its association with gastro-intestinal disease, achlorhydria and haemorrhage

BY

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This communication deals principally with the occurrence of iron-deficiency anaemia in children who have passed the period of infancy, in whom factors other than those commonly causing infantile nutritional anaemia have played a part. The common causes of nutritional anaemia have been classified by Mackay13 and Parsons et al19, and amongst these are some which may also affect older children; further facts concerning the causation of iron-deficiency anaemia after infancy, its relation to other morbid processes and its association with achlorhydria and chronic intestinal disease are now reported.

Haematological criteria of iron deficiency.—Since iron is essential for the formation of haemoglobin, failure of the organism to obtain a sufficient supply leads to diminished production of haemoglobin. The first stage in this is shown by a fall in the haemoglobin content of the cells. More serious degrees of iron deprivation result as well in a diminished output of erythrocytes, always proportionally less than the hypochromia, so that it is common to find that when the anaemia is severest the haemoglobin saturation of the cells is lowest. When iron therapy is instituted the following changes occur in the peripheral blood: first, a reticulocytosis, which reaches its maximum at the end of about a week and then with recovery, slowly falls to normal; secondly, a rise in the erythrocytes to slightly above normal; thirdly, a slow rise of haemoglobin to normal; and finally in some cases a slight reduction in the number of circulating red cells (Hagen’s phenomenon). The changes in the diameter of the red cells have been shown to be the same in infantile nutritional anaemia19 as those described by Price-Jones in the idiopathic microcytic anaemia of adults21; there is a microcytosis which diminishes with recovery, the process being accompanied by an increased variability while this is taking place. The diminution in mean corpuscular

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volume observed by Vaughan and Goddard has been noted in cases to be quoted in this paper. Since no other substance causing these changes, and resulting in the recovery of the anaemia, has been found, it is reasonable to assume that in cases of doubt the evoking of the response by iron therapy, reticulocytosis in particular, may be used in final confirmation of the diagnosis.

Other haematopoietic factors may be deficient as well as iron, and the response will then be incomplete; in cases where iron is not deficient, the response will be absent. It has been stated that iron, quite apart from its rôle as an integral part in the haemoglobin molecule, may act as an erythropoietic stimulant even although there is no deficiency. We, ourselves, have not produced a reticulocytosis in normal infants with therapeutic doses of iron, though Barr using massive doses claims to have done so.

Achlorhydria.

Though achlorhydria is recognized as a feature of idiopathic microcytic anaemia of adults, so that Witts demonstrated either absence or extreme reduction of hydrochloric acid in the fractional test-meals of 81 per cent. of his series of adult women, yet investigators of the nutritional anaemia of infants have not so far attempted to establish any disorder of gastric function in their cases. Knowledge of the normal gastric function in infancy is incomplete, but in health, after four weeks, hydrochloric acid is secreted at all ages.

Recently we have begun to investigate the gastric function of cases of simple iron-deficiency anaemia by the method of the fractional (alcohol) test-meal. In twelve of thirteen successive patients, whose ages ranged from eight months to ten years, achlorhydria was found (see table 1).

<table>
<thead>
<tr>
<th>TABLE 1. TWELVE CASES OF IRON-DEFICIENCY ANAEMIA ASSOCIATED WITH ACHLORHYDRIA.</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>PATIENT.</td>
<td>AGE.</td>
<td>PRESUMED AETIOLOGICAL FACTORS.</td>
</tr>
<tr>
<td>J. D. (Case 1)</td>
<td>8 months</td>
<td>Prematurity and possibly iron-deficiency in the mother.</td>
</tr>
<tr>
<td>R. S. (Case 2)</td>
<td>13 months</td>
<td>Prematurity, malnutrition.</td>
</tr>
<tr>
<td>E. M.</td>
<td>15 months</td>
<td>Prematurity, malnutrition.</td>
</tr>
<tr>
<td>F. M.</td>
<td>19 months</td>
<td>Refusal of practically all foods except milk with consequent undernutrition.</td>
</tr>
<tr>
<td>A. P.</td>
<td>1 yr. 11 mth.</td>
<td>Breast fed 11 months, then dried milk 3 months: appetite always poor.</td>
</tr>
<tr>
<td>M. P.</td>
<td>Twins</td>
<td>Twin-gestation.</td>
</tr>
<tr>
<td>R. P.</td>
<td>2 years</td>
<td>Had been on a mixed diet which may have been insufficient: history of haemorrhage after tonsillectomy some considerable time previously.</td>
</tr>
<tr>
<td>W. S.</td>
<td>3 yr. 8 mth.</td>
<td>Home diet inadequate; anaemia appeared to have persisted on the diet of a hospital for infectious diseases (7 months).</td>
</tr>
<tr>
<td>T. H. (Case 3)</td>
<td>4 yr. 2 mth.</td>
<td>Diet inadequate since birth.</td>
</tr>
<tr>
<td>R. K.</td>
<td>5 yr. 6 mth.</td>
<td>Causation unknown: diet good.</td>
</tr>
<tr>
<td>M. H.</td>
<td>6 years</td>
<td>Causation unknown: diet good.</td>
</tr>
<tr>
<td>P. F. (Case 4)</td>
<td>9 yr. 6 mth.</td>
<td>* Case records follow.</td>
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</table>
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In three cases achlorhydria was still present a year or more after cure by iron. Four of these twelve cases have been selected in illustration of the achlorhydria which may accompany iron-deficiency anaemia at various periods of childhood.

Case 1.—Simple iron-deficiency anaemia associated with persisting achlorhydria.

J. D., a male aged eight months, was admitted for 'jaundice.' His mother had been treated for anaemia of some years' duration; the patient was a premature baby, weighing three lb. at birth. He was breast fed for one month and then given Nestle's milk and Cow and Gate. A week before admission, after a simple acute infection, a yellow pallor was noticed. On examination he was a well-nourished, pallid infant, with Harrison's sulcus, a 'rachitic type' head, enlarged spleen, no jaundice, and normal bone x-ray.

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<td>15, 17, 21, 25, 29</td>
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<td>18, 30</td>
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Fig. 1.—J. D.

Note: All haemoglobin investigations by Haldane's method.

Gastric analysis. An alcohol test-meal showed an absence of free hydrochloric acid.

Sequel. Adequate clinical improvement observed; gain in weight. Disappearance of splenomegaly. Achlorhydria still found after four months. Achlorhydria after injection of histamine (0·05 mgm.) was also observed in this case.

Case 2.—Simple iron-deficiency anaemia associated with persisting achlorhydria.

R. S., a male aged thirteen months, was admitted to hospital for anaemia with a history of increasing pallor for two months. He was one month premature, birth weight six lb. He had been breast fed for three weeks, and then fed on diluted cow's milk until eight months old, followed by eight months of practically no solids, without gravy and green vegetables, but he received Robinson's Groats and stewed fruit in
addition to milk. He was a pallid child, yellow tinted, with the spleen not palpable and no jaundice.

The child was discharged before complete recovery had taken place.

**GASTRIC ANALYSIS.** An alcohol test-meal during his stay in hospital showed a complete absence of free hydrochloric acid.

**SEQUEL.** A year later there was no pallor, but on gastric analysis free hydrochloric acid was still absent and a Price-Jones curve showed a tendency to microcytosis (mean cell diameter 6.762 μ).

**Case 3.—IRON-DEFICIENCY ANAEMIA ASSOCIATED WITH POVERTY AND ACHLORHYDRIA.**

T. H., a male aged four years and two months, was admitted to hospital for anaemia. The mother stated that he had always been pale and inadequately fed on account of poverty. He was breast fed for the first three months and then received dried milk. He had not ailed until he developed scarlet fever eight months before admission. He was in an isolation hospital for seven months and was then referred
to us by the London County Council. He was sallow with pale mucosae, thin and apathetic, with a slightly enlarged heart and a mitral systolic murmur widely propagated. The spleen was not palpable.

**Gastric Analysis.** An alcohol test-meal during his stay in hospital showed a complete absence of free hydrochloric acid.

**Sequel.** A year after he came under observation he was re-examined. He was no longer pale, but was well-grown, with a slight degree of microcytic anaemia as shown by haemoglobin estimation and a Price-Jones curve (mean cell diameter 6.655 μ). Gastric analysis showed that absence of free hydrochloric acid had persisted.

**Case 4.—Iron-deficiency anaemia with achlorhydria two years after complete recovery.**

P. F., a female aged nine-and-a-half years, was admitted for the investigation of anaemia. She was born in India and breast fed for thirteen months, being brought to live in England at one year and nine months. She had a good home and good feeding. Pallor and languor had been present for six weeks. There was loss of appetite and disinclination for work or play. She was a well-grown child, mentally alert, with no wasting. Pallor of skin and mucous membranes was present with a haemic murmur at cardiac apex. The abdominal viscera were normal to palpation.

She was treated first as an in-patient and subsequently at home, making a slow but complete recovery on a mixture containing ferri perchlor. n v, with liquor arsenicalis hydrochlor. m ij. A month after the beginning of treatment liver extract was introduced.

**Fig. 4.—P. F.**

**Sequel.** When re-examined two years after recovery there was no anaemia, but an alcohol test-meal demonstrated absence of free hydrochloric acid although she appeared to be in robust health.

Though the number of cases investigated by this method is small, we regard persistence of achlorhydria after apparent recovery as probably significant in the aetiology of the anaemia, especially in view of analogous findings in the idiopathic microcytic anaemia of adults. Confirmation of our findings needs to be obtained by similar observations in a larger series of cases and we are continuing to investigate patients by gastric analyses, employing histamine in some.

**Anaemia associated with intestinal disease.**

The following are two cases of anaemia in which an intestinal polypus was unexpectedly discovered at autopsy, no melaena having occurred to suggest the diagnosis. Are intestinal polypi and analogous conditions
too easily overlooked as causative lesions in certain cases resembling nutritional anaemia?

Case 5.—Anaemia with Intestinal Polypus and Incomplete Response on Iron-Therapy.

J. R., a female of ten months, was admitted for anaemia, bronchitis, and loss of weight. It was stated that she had always been pale, and that she had nearly died of bronchitis and pneumonia five weeks previously. Since this illness the anaemia had increased. Though she had been a full-time baby, breast fed throughout, she had gained weight slowly. She was a well-nourished, anaemic baby with a systolic cardiac murmur and the spleen was not enlarged. A week after admission diarrhoea and vomiting set in without naked-eye blood in stools. Subcutaneous salines were required to combat dehydration. Death from gastro-intestinal disorder took place four weeks after admission.

**Fig. 5.—J. R.**

Post-mortem. The findings were those of anaemia and toxaemia, together with the discovery of a polypus in the small intestine; both middle ears contained pus. The tissues generally were pale; the heart was pale and dilated; the liver and kidneys were pale and fatty. In the small intestine, eight feet above the ileo-caecal valve, was a firm round polyp as big as a walnut, and covered with a rugose mucous membrane.

Case 6.—Anaemia with Intestinal Polypus and Congenital Heart Disease.

P. S., a female aged five years, was admitted for convulsions and congenital heart disease. A congenital heart lesion was recognized when she was five months old. Attacks of unconsciousness, preceded by abdominal pain, had occurred for a few months. She was a pale, well-nourished child, with congenital morbus cordis without cyanosis. The spleen was not palpable. Haematology: 21.1.33—R.B.C. 4.52 mill., Hgb. 63 per cent., reticulocytes 3.9 per cent. (eight days after beginning of iron-therapy). 30.1.33—R.B.C. 4.2 mill., Hgb. 72 per cent., reticulocytes 0.5 per cent.

Sequel. She was admitted to the East Ham Memorial Hospital ten months later, having, for a week, passed large quantities of blood per rectum. A blood transfusion of 800 c.c. was given; despite this she died.

Post-mortem. A large ulcerated pedunculated polypus was found in the sigmoid colon, and a patent ductus arteriosus was present.
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In each of these cases ordinary iron-deficiency anaemia was diagnosed and this opinion was supported when on iron therapy a haematological response was seen. Nevertheless, recovery was not obtained perhaps, in one case at least, because occult haemorrhage continued from a polypus the presence of which had not been suspected during life. Conditions other than polypus, by producing long-continued occult haemorrhage, are known to result in an anaemia which responds to iron. In ulcerative colitis for example a similar anaemia may be observed, partly due to haemorrhage, sometimes manifest as melaena.

Case 7.—SEVERE ANAEMIA RESPONDING TO IRON AND BLOOD TRANSFUSION, ASSOCIATED WITH ULCERATIVE COLITIS.

D. B., a male aged two years and nine months, was admitted for 'colitis and melaena.' Nine weeks previously bouts of illness had begun in which he passed blood and slime. The stools were about six a day. He was well-nourished, pale, with a haemic murmur, and no enlargement of spleen. All investigations as to aetiology of 'colitis' were negative. He was readmitted at the age of three years and eleven months on account of a relapse of symptoms, worse than on the previous occasion having passed fifteen stools, mostly blood. In addition to medical treatment he received a whole blood transfusion of 360 c.c. with beneficial results. Readmitted aged four years and eight months, after numerous relapses the patient showed a further response to medical treatment which was very slow and relapses occurred. Blood transfusions seemed beneficial. He was readmitted aged five years and one month for severe secondary anaemia. The patient appeared pale and apathetic, with fair nutrition, and having diarrhoea with blood and mucus. The anaemia responded to iron therapy, the haemoglobin rising from thirteen to fifty-eight per cent. (fig. 6). At this stage relapses due to further haemorrhage occurred necessitating subsequent transfusion; eventually a haemoglobin reading of 70 per cent. was reached.

Instances of so-called 'ulcerative colitis' such as the one just described illustrate the fact that any given anaemia may have its cause in a number of circumstances. Contributing to the iron-deficiency discovered in this child were factors such as the invalid diet used in the treatment of his complaint, the intestinal lesions and chronic diarrhoea which probably hindered intestinal absorption, and also the long-continued intestinal bleeding so characteristic of the condition. It may be noted that our knowledge of the pathology of similar cases of intestinal haemorrhage is unsatisfactory. In the present instance the source of the bleeding was not located.
Intestinal factors are known to play the leading part in the anaemia of coeliac disease. Iron deficiency is commonly present, and results in a microcytic type. Megalocytic anaemias responding to liver and marmite have been recognized, particularly in the older cases. The following cases were characterized by severe hypochromic anaemia, but not by achlorhydria.

**Case 8.—Severe anaemia associated with coeliac disease.**

E. W., a male aged seven years, was admitted for abdominal pain and vomiting, having been 'yellowish' for six months. He was the third in a family of four, an elder sister having also suffered from coeliac disease. (This sister was also admitted and the diagnosis confirmed.) Abdominal pain and vomiting had occurred for a period of two years. He had been anaemic and apathetic for six months, the bowels being constipated except during attacks, when the stools were light, loose and offensive. He showed great asthenia with dark pigmentation of scars and exposed areas of which the cause was not explained. The spleen was enlarged. The van den Bergh reaction was normal. A stool contained split fat 62.4 per cent., unsplit fat 3.95 per cent., total fat 66.43 per cent. Microscopically, large excess of fatty acid crystals were found.

### TABLE 2.

<table>
<thead>
<tr>
<th>Date</th>
<th>R.B.C. (Millions per c.m.m.)</th>
<th>Haemoglobin per cent. (Haldane)</th>
<th>Colour Index</th>
<th>Reticulocytes (per cent. of R.B.C.)</th>
<th>W.B.C. per c.m.m.</th>
<th>Treatment</th>
<th>Notes</th>
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<tbody>
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<td>4.8.32</td>
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<td>Poik; An; P.B.;</td>
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<td>22.8.32</td>
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<td>1.25</td>
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<td>—</td>
<td>—</td>
<td>—</td>
<td>100 W.B.C.</td>
<td></td>
<td>100 W.B.C.</td>
</tr>
</tbody>
</table>

**Notes:**

- An; Poik; Poly;
- 1 Normoblast/
- 100 W.B.C.
- Platelets:
- 82,900/c.mm.
- Poik; An; Poly;
- P.B.;
- Pulv. Ferri Carb. Sacch. gr. v t.d.s.
- Price-Jones' Curve—Mean Cell Diameter
- 7.3235 μ
- Price-Jones' Curve—Mean Cell Diameter
- 7.354 μ

**Price-Jones' Curve—Mean Cell Diameter**

- 7.3235 μ
- 7.354 μ

**Notes:**

- An. = Anisocytosis
- Poik. = Poikilocytosis
- Poly. = Polychromasia
- P.B. = Punctate basophilia
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GASTRIC ANALYSIS. An alcohol test-meal showed figures within the limits of normal acidity.

SEQUEL. He received orthodox treatment for coeliac disease over a long period in the country branch hospital at Tadworth, and behaved in the manner characteristic of his disorder.

**Fig. 7.**—Coeliac rickets, osteoporosis, healing (spontaneous) fractures. (Case 9.)

**Case 9.**—Severe anaemia with coeliac disease and rickets.

K. A., a female aged twelve years when first admitted to hospital for coeliac disease. She weighed only three lb. at birth and was physically backward during infancy. Until four-and-a-half years ago her health was stated to be good. Since that time she had been subject to attacks of vomiting of a week's duration and abdominal pain. The stools had often been pale, loose and frequent, though she had
also had periods of constipation. The symptoms had been growing worse for the last six months and her legs had been weak, so that she required to be carried up and down stairs. She was anaemic and stunted. Her height was 42 in. (average at twelve years being 57 in.); her weight was 35 lb. (average weight at twelve years being 81 lb). Radiological examination showed numerous spontaneous fractures in various stages of healing, and rickety changes in the epiphyses (fig. 7). The blood serum calcium was 6-6 mgm. per cent. (normal 9 to 11), and the inorganic blood phosphorus 2-9 mgm. per cent. (normal 4 to 5-5). The stools were greasy and their analysis showed:-split fat 47-2 per cent., unsplit fat 18-1 per cent., total fat 65-3 per cent.

GASTRIC ANALYSIS. An alcohol test-meal demonstrated the presence of small amounts of free hydrochloric acid during the first twenty minutes but not subsequently. Orthodox treatment for coeliac disease was instituted. She improved very gradually, and gained weight, the total fat in the stool eventually falling to 42-8 per cent. The response to haematological treatment is shewn in fig. 8. Iron therapy raised the haemoglobin from 30 per cent. to 54 per cent. and then recovery was checked until hepatopsin (intramuscular), and later liver extract, were employed. Eventually complete restitution of the blood picture was seen.

Anaemia associated with other diseases.

In a great number of other diseases iron deficiencies may arise. We have seen haemolytic anaemias of various types show a latent iron deficiency unmasked during their recovery. This may occur, for example, in the haemolytic anaemias of the neontal period, in Lederer's anaemia, von Jaksch's anaemia, and also in splenic anaemia and we have seen the characteristic response to iron in some cases of anaemia accompanying congenital syphilis, rickets and cardiac rheumatism.
Discussion.

In the aetiology of the nutritional anaemia of infancy, which we prefer to call iron-deficiency anaemia, factors such as prematurity, twin-gestation, hypochromic anaemia in the mother, over-prolonged milk feeding and defective diet, are well recognized. Though its clinical appearance may be similar, the analogous iron-deficient state seen after the age of infancy would appear to have a somewhat different background. Often the anaemic aspect forms part of the clinical picture of some chronic condition; more occasionally it may be seen in an acute disease, particularly when treated by strict diet or associated with much anorexia. Gastro-intestinal disorders would appear to be more directly related, and we have shown that achlorhydria may be a causal factor. It may be questioned whether the achlorhydria which we have demonstrated in certain cases was post hoc or propter hoc, and indeed the same point was raised, and settled, concerning the adult cases of idiopathic microcytic anaemia. The persistence of the achlorhydria after successful treatment of the anaemia and the tendency to anaemic relapses have been taken as evidence that the acid deficiency is not secondary to the anaemia. We have proved the persistence of acid deficiency in those of our achlorhydric patients who have been cured for a year or more. Iron absorption is held to depend largely on the activity of the acid gastric secretion which converts food-iron into ferrie and ferrous chlorides. The conditions for absorption of these salts are at their optimum in the duodenum when its contents are acid. The secretion of hydrochloric acid is not essential for the absorption of iron and increased ingestion of iron may make up for an acid deficiency. This provides the explanation for the clinical success of adequate iron therapy. Nevertheless, achlorhydria is probably as much an indication for the use of hydrochloric acid as an adjuvant in the iron-deficiency anaemias of childhood as it is in those of the adult.

With regard to the iron-deficient states seen in infants, there are still problems of causation which await solution. For example, not all cases of nutritional anaemia are to be satisfactorily explained by the recognized causative factors mentioned above. From time to time anaemic infants are encountered who have been born of healthy mothers, at full time, breast-fed and remain outwardly free of disease. Such cases led Czerny to postulate a constitutional anomaly by which he also explained the fact that, of two infants under similar conditions, one might develop an anaemia and the other not. This standpoint was supported by Kleinschmidt and others under designations such as 'hereditary predisposition' and 'functional weakness of the blood-forming organs.' Mackay finds these explanations inadequate on the one hand and vague on the other, and for these anomalies prefers to postulate the possibility of deficient iron-storage in the liver.
wasteful utilization, or even some unknown controlling factor comparable with calciferol in the metabolism of calcium and phosphorus. The position may be simplified by considering the physiology of iron-absorption in these cases.

Numerous observations on the gastric acidity of infants have shown that the pH may be expected to vary during digestion according to the nature of the feed, and the health and growth of the infant. Undernutrition and most forms of illness, particularly those of an infective nature, are commonly accompanied by a lowered acidity\textsuperscript{4, 14, 18} and in infancy the total average volume of secretion is remarkably small in comparison with that found at later ages of childhood\textsuperscript{17}.

Under experimental conditions, Bauer\textsuperscript{2} showed that gastric juice dissolves iron and that the amount dissolved varies with the pH. Further, Mettier and Minot\textsuperscript{16} have supplied clear evidence that acid assists in the absorption of iron. The large doses of inorganic iron salts required for the cure of iron-deficiency anaemia in achlorhydric persons suggest that human subjects are physiologically economical with their food-iron by virtue of secretion of hydrochloric acid in sufficient quantity. It is even possible that for ordinary physiological requirements ferrous chloride is the only form of iron which is absorbed. In practice achlorhydria, and hypochlorhydria in less degree, may unmask a relative shortage of iron-intake, and vice versa.

It has been shown that minor degrees of iron-deficiency anaemia are common in infants both breast- and bottle-fed\textsuperscript{13}. Setting aside natal and prenatal causes, such as prematurity, twin-gestation, etc., it has been found that this deficiency anaemia is more common, and usually more severe, in artificially-fed than in breast-fed infants. Differences in the pH of the gastric contents of infants digesting breast and cow’s milk have been established by Marriott and Davidson\textsuperscript{14}, who found that infants fed on cow’s milk had a higher average pH (lower acidity) due to the ‘buffer effect’ of cow’s milk protein. Compared with breast-milk feeding they found that the effective concentration of acid was less than one-twentieth. These results were later confirmed by the figures which Wills and Paterson\textsuperscript{25} reported. In this fact is an explanation of Blauberg’s\textsuperscript{4} observation that iron retention is less on cow’s milk than on human milk. When it is recalled that the iron content of cow’s milk is less than that of human milk [cow’s milk 0·00024 per cent. (Peterson and Elvehjem), human milk 0·0008 per cent. (Dorlencourt and Calugareanu-Nandris\textsuperscript{13})] we have another reason why anaemia is relatively more common with cow’s milk feeding, though it is doubtful if the difference in iron content is sufficient explanation to serve alone; indeed it is likely that the question of percentage retention is the more important. Certain other facts, such as the occurrence of anaemia in otherwise normal and breast-fed infants, may be accounted for by individual differences in percentage-absorption, as hinted by Mackay, and particularly in gastric-secretion, as suggested by this paper.
The relation between acid deficiency during digestion and the occurrence of iron-deficiency anaemia is discussed, first, in children past the age of infancy, and secondly, in infants. Cases illustrating the achlorhyria which may be found in association with this type of anaemia are briefly described. Of the many gastro-intestinal disorders besides achlorhydria which may contribute to anaemia in children examples are reported of intestinal polypus, of so-called 'ulcerative colitis,' and coeliac disease.

Severe and apparently causeless anaemias, which respond wholly or partially to iron therapy, demand attention to the state of the gastro-intestinal tract. Haemorrhage from the intestine, sometimes occult, sometimes manifest, and digestive, as well as absorptive failures, may each present themselves in the guise of severe anaemia.

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Iron-deficiency anaemia in children: Its association with gastro-intestinal disease, achlorhydria and haemorrhage

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