procedure this operation has its justifications, but it is questionable if it will appreciably increase life expectancy. It is yet too early to form a final judgment. Further reports on the progress of these children will be awaited with interest.

Summary

Surgery can obliterate the patent ductus arteriosus and eradicate the congenital stenosis of the distal aortic arch known as coarctation of the aorta. The clinical diagnosis of these defects is discussed. The diagnosis of coarctation of the aorta is missed repeatedly in childhood by a failure to palpate the groins as a routine procedure. Feeble or absent femoral pulses make a characteristic finding. An account is given of four children in whom this defect was observed. Diagnosis of these congenital flaws within the first ten years of life is important if full advantage is to be taken of current surgical procedures designed for their correction.

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RESISTANT ANAEMIA

A NOTE ON THE DIFFERENTIAL DIAGNOSIS OF PERNICIOUS ANAEMIA AND FAMILIAL ACHOLURIC JAUNDICE

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The purpose of this communication is to draw attention to the not uncommon error of confounding familial acholuric jaundice (F.A.J.) with pernicious anaemia (P.A.), and to show how that mistake may arise and how it can be avoided. Acholuric jaundice is usually regarded as a rare condition; but we are inclined to think that its supposed rarity is largely due to its being frequently overlooked. During the last fourteen months we have seen no fewer than nine previously undiagnosed cases of acholuric jaundice, each one belonging to a separate family. They were, in fact, numerically in excess of the new cases of true pernicious anaemia with severe anaemia seen during the same period. Among such cases of pernicious anaemia we do not include those suffering from a greater or lesser degree of P.A.-factor deficiency secondary to some other disease such as sprue, carcinoma of the stomach, or liver cirrhosis; nor do we include cases suffering primarily from symptoms of subacute combined degeneration of the cord with a slight or negligible degree of anaemia. Now, of our nine cases of acholuric jaundice no fewer than four had been diagnosed as pernicious anaemia and treated as such for periods up to as long as five years. In a much larger series of cases seen prior to 1940 this same mistake was noted in a somewhat similar proportion; but owing to the loss of part of the card index during the war the details of that series are not available. The present note will therefore refer only to cases seen since October, 1944. Though the series is a small one, the figures we have just given clearly show that the disease acholuric jaundice and the mistake to which we refer are common enough to merit attention.

The Clinical Picture

Clinically, familial acholuric jaundice, with its anaemia and icterus, bears a close resemblance to pernicious anaemia.

Jaundice.—In F.A.J. there is usually slight or moderate icterus, but it may be very marked, and occasionally it is absent. In the latter case a history of one or more previous attacks of yellowness may be obtained. In this connexion one must bear in mind the frequency with which pigment stones occur in F.A.J., giving rise to attacks of gall-stone colic or obstructive jaundice. One of our cases was admitted to hospital deeply yellow as a result of biliary obstruction; and it was only during the routine examination of the blood picture that the underlying cause of the condition was shown to be F.A.J. In another case a cholecystectomy had been performed ten years before on account of two attacks of jaundice and biliary colic; but the significance of the pigment stones which were found was not appreciated.

Splenomegaly.—Sometimes a gross splenomegaly will exclude P.A. and indicate the true diagnosis. But frequently the spleen is not palpable in F.A.J., and very often it is no more easily palpable than in many cases of P.A. In one of our cases showing all the other characteristics of F.A.J. there was no increase in the size of the organ when it was examined at operation.

Ulceration of the Legs.—When there is chronic ulceration of the legs, or a history of such ulceration, in association with anaemia the diagnosis is beyond doubt; unfortunately, leg ulcers probably occur in less than 20% of the patients, though in this short series it was seen in over 40%. The ulcers usually occur at a higher level than those associated with varicose veins, though sometimes they are found round the ankles over the malleoli. Often affecting the middle of the leg, they may lie anteriorly or posteriorly, and tend to spread slowly but remorselessly. They are usually intensely painful and are resistant to all local treatment, although they tend to heal during prolonged rest in bed. Splenectomy, which abolishes all the symptoms of F.A.J., results in the healing of the ulcers in about six weeks.

Family History.—A family history of anaemia, and more particularly of jaundice, or of ulceration of the legs, is very suggestive. Yet often one can obtain no such history even after diligent questioning; while, on the other hand, one must avoid being misled by the not uncommon story that "anaemia runs in the family," and by the fact that occasionally patients with P.A. give a family history in which jaundice as well as anaemia plays a prominent part. One of our patients told us that her brother had died of leukaemia, and another that her mother and brother had succumbed to splenic anaemia. Investigation made it clear that in both these families the deaths had been due to F.A.J. Five out of our nine cases gave a relevant family history.

Periodicity.—Another point which may help in the clinical diagnosis is the story of the periodic nature of the attacks of anaemia and yellowness. This seldom happens in P.A. unless the patient has received intermittent treatment with liver. But so many of the cases of F.A.J. which one sees are in their first "attack" and give no history of previous ones.

Age.—It must be emphasized that the signs and symptoms of F.A.J. often remain latent till late in life. Thus five of our patients were over 50 when their first symptoms appeared, three were over 60, and one was over 70.

Alimentary and Nervous Signs.—Other aids to the clinical differential diagnosis consist in the presence or absence of the signs and symptoms referable to the alimentary and central nervous systems which are so frequently present in P.A. But whereas the history or presence of such signs and symptoms when well marked is highly suggestive of P.A., their absence by no means excludes that disease. It must be remembered that glossitis occurs in many other conditions apart from P.A.; and that "pins and needles" in the hands or feet, which is perhaps the commonest early symptom of subacute combined degeneration of the cord, may be found in any severe anaemia, presumably as the result of peripheral anoxaemia. It is worth noting, in this connexion, that "pins and needles" due to an anaemia *per se* is likely to be perfectly symmetrical in distribution; while a definite asymmetry, with the tingling more pronounced on one side than another, is more suggestive of an organic, and presumably neurological, lesion. It cannot be too strongly emphasized how important it is in every suspected case of P.A. to have a fractional test-meal examination.

If any free acid is found it is absolutely certain that the case is not P.A.—at least, not one of the primary Addisonian type. On the other hand, the absence of free acid, though strongly suggestive of P.A., does not completely exclude F.A.J. Thus in the six of our cases in which it was practicable to carry out a test-meal examination there was an absence of free acid in two.

The Blood Picture

It is not only the clinical picture which may confuse the practitioner, for the haematological picture, at least in its elementary form, may be even more misleading. The reason for this is that most cases of F.A.J. have a high colour index. It is seldom much below unity, it is often well above unity, and it is occasionally higher than in any other disease. Unfortunately, a colour index definitely above unity is popularly regarded as pathognomonic of P.A. or of one of those rare macrocytic anaemias which differ from P.A. only in their failure to respond to liver.

For perhaps the majority of clinicians the blood picture as regards the red cells is complete if a red cell count and haemoglobin estimation are done. These two figures, together with their quotient the colour index, are all the information that is considered. The remarks of the pathologist as to the degree of anisocytosis, anisochromia, poikilocytosis, etc., tend to be regarded as little more than frills to lend some semblance of complexity to an otherwise simple report. A reticulocyte count and a measurement of the mean diameter of the red cells seem to be looked upon as a luxury barely worth the extra trouble. Yet it is chiefly upon these three pieces of information—the mean cell diameter and its relation to the colour index, the appearance of the red cells in stained films, and the reticulocyte count—that the successful differential diagnosis between F.A.J. and P.A. depends.

Colour Index and Mean Cell Diameter.—Whereas the colour index is usually high in both F.A.J. and P.A., the mean cell diameter is generally much increased in P.A. and much diminished in F.A.J. This apparent discrepancy—a high colour index with a small mean cell diameter—is one of the most characteristic points in the blood picture of F.A.J. Usually the mean cell diameter is smaller than in any other condition—often less than 6μ ; yet the colour index is around unity or even above it. Less commonly, the mean cell diameter is only slightly reduced, when the colour index will be well above unity. Finally, in rare cases the mean cell diameter is actually above normal, and then the colour index may reach extraordinarily high values. The reason for this is the spheroidal shape of the cells, which results in their surface area and volume being much larger in proportion to their diameter than is the case with normal red cells, with their comparatively thin disk-like figure. This sort of discrepancy is seen only in F.A.J. In P.A. one occasionally gets a discrepancy in the opposite direction—a large cell diameter with a low colour index—due to a post-haemorrhagic anaemia being superimposed on the macrocytosis. This will happen when there is some incidental cause of blood loss such as haemorrhoids, or when the thrombocytopenia associated with P.A. is sufficiently developed to produce a haemorrhagic purpura.

The Appearance of the Red Cells in Stained Films.—Irregularities in the size, staining, and shape of the red cells tend to be well marked in the majority of severe anaemias. They are absent or but slightly noticeable only in those severe anaemias that are due to an aplasia of the bone marrow or which are associated with toxic or infective processes where there is presumably some general depression of bone-marrow function. Now, while it is fully realized that the extent to which these abnormalities of the red cells are developed gives a rough indication of the degree of marrow activity, it is not usually appreciated that a more subtle analysis of these abnormalities will often supply us with information of the greatest diagnostic value. In particular it is by close attention to the detailed appearance of the red cells in stained films that one most readily avoids the mistake of muddling F.A.J. with P.A. In the majority of anaemias where there is gross irregularity in the size of the red cells there is also great irregularity in their shape, and this is especially true in P.A. But in F.A.J. one of the most striking features is that although the cells have an enormous range in size they are extraordinarily uniform in

shape, being almost perfectly circular disks: there is, in fact, gross anisocytosis without poikilocytosis. Again, irregularity in the depth of staining of the cells, "anisochromia," is by no means uncommon in severe anaemias. Usually it is what one might call "irregular" in type—that is to say, many of the large cells are pale and many are dark—while the same is true of the small cells. In a typical case of P.A. there is usually little or no anisochromia, all the cells being fairly completely and uniformly filled with haemoglobin. In severe hypochromic anaemias there is again little or no anisochromia; but here the cells are very deficient in haemoglobin and appear uniformly pale. However, in cases of hypochromic anaemia and P.A. under treatment with iron and liver respectively, when the haemoglobin production tends to lag behind the cell formation, the anisochromia often becomes very striking. If there is any tendency towards regularity in the anisochromia of P.A. under treatment, it is that the larger cells tend to be more completely filled with haemoglobin and to appear pinker than the smaller cells. But in F.A.J. the picture is quite different: the anisocytosis and anisochromia are of striking regularity, the great majority of the small cells staining deeply and the large cells palely. *There is no other condition in which this happens*; and usually the appearance is so remarkable that one look at the stained film without any other examination, haematological or clinical, is sufficient to make one extremely suspicious of the correct diagnosis.

Reticulocytes, Stippled Cells, and Diffuse Basophilia.—Although a gross reticulocytosis is in no sense pathognomonic of F.A.J., it is nevertheless a feature which distinguishes absolutely between that disease and P.A. In a severe untreated case of P.A. the reticulocytes are usually not increased above the normal 1 to 1½% of the total red cell count, and they seldom if ever exceed 2 or 3%. In a case of F.A.J. in which the anaemia is severe there is always a gross reticulocytosis: it is usually at least 15 to 20%, and often 40 to 50% or even much higher. One must of course beware of the severe case of P.A. which has recently received an injection of liver, so often administered before the diagnosis is established. Although a high reticulocytosis may occur in any of the other haemolytic anaemias, such as lead-poisoning, and to a less extent after an acute haemorrhage, in hypochromic anaemia under treatment with iron, in certain types of leukaemia, and in leuco-erythroblastic anaemia the other haematological characteristics of F.A.J. will be missing, while features peculiar to these conditions will usually be present.

A small percentage of stippled cells are usually to be seen in P.A.; but in F.A.J., though there is a gross reticulocytosis, few if any of these cells appear as stippled cells with Romanovsky stains. Many of the reticulocytes in F.A.J. appear bluish (diffusely basophilic) in the Leishman-stained films. This supplies another feature which may help in distinguishing the disease from P.A. When diffuse basophilia is well developed in F.A.J. as many as 10 or 20% of the cells may have a bluish tint, whereas in P.A. the figure never reaches 1% of the total cell count.

Nucleated Red Cells.—Nucleated red cells are usually present in both P.A. and F.A.J., and may occasionally reach high figures; but the type of nucleated cell is very different in the two conditions. In P.A. these cells are of all degrees of immaturity; in F.A.J. the vast majority of them are late-type cells with solid-looking, structureless nuclei. Moreover, these pyknotic nuclei frequently assume bizarre shapes not often seen in other diseases, being double-lobed, triple-lobed, or even mulberry-like in appearance.

The White Cells.—In F.A.J., when the anaemia is marked, there is usually a polymorphonuclear leucocytosis with a left shift, both of which may be considerable. In P.A., on the other hand, there is nearly always some degree of leucopenia due to reduction in the polymorphonuclears; while among the granulocytes which remain there are not only immature cells, which may include myelocytes and even metamyeloblasts, but also some very large polymorphonuclears with highly complicated lobulation of their nuclei: a shift simultaneously both to left and to right.

In Table I we have summarized the main differences in the blood pictures of F.A.J. and P.A., and in Table II the clinical features of our nine cases of F.A.J.

TABLE I.—*Main Differences between the Blood Picture of Acholuric Jaundice and that of Pernicious Anaemia*

	F. A. J.	P. A.
Colour index	High	High
Mean cell diameter	Low	High
Anisocytosis	Marked	Marked
Poikilocytosis	Absent	Marked
Anisochromia	Marked and regular	Slight
Stippling	Absent	Moderate
Diffuse basophilia	May be gross	Moderate
Reticulocytosis	Extreme	Absent
Nucleated red cells	Late type	All types
White cells	Leucocytosis	Leucopenia

It must be realized that the above remarks apply only to cases of F.A.J. and P.A. which are in an active phase of the disease. In cases of F.A.J. with but a mild degree of anaemia, or which are discovered during the routine examination of an acholuric family, the above characteristics will naturally be less well developed; but even in such cases some or all of them are generally fairly obvious.

Fragility.—So far we have refrained from any reference to fragility of the red cells because we have been concerned only with the more elementary points in the diagnosis. We maintain that the determination of the fragility of the red cells,

ated with clinically recognizable jaundice, demands painstaking clinical and laboratory work. The ultimate justification for this labour must be the availability of successful treatment. This is presented in splenectomy. In skilled hands the operation is not hazardous, for the spleen is never bound down by adhesions as in splenic anaemia. Although it is desirable by means of blood transfusion to raise the haemoglobin to a reasonable level before operation, it is sometimes impracticable to achieve this ideal owing to the rapidity of the red cell destruction going on in the body. In such cases, rather than delay too long it is better to operate at a comparatively low haemoglobin level and to give a further transfusion of blood immediately after the operation. It is remarkable how rapidly in most cases the haemoglobin rises when once the spleen is removed. In one of our cases a two-pint (1.14 l.) transfusion of fresh blood raised the haemoglobin only from 40% to 45%; splenectomy was then performed, being followed immediately by the giving of two further pints of blood, and within 24 hours the haemoglobin had risen to 70%.

Summary

The frequency with which familial acholuric jaundice is wrongly diagnosed and treated as pernicious anaemia is emphasized.

The commonest causes of this mistake have been found to be:
(1) An unfounded belief in the diagnostic value of the colour index.

TABLE II.—*Chief Clinical Features of 9 Cases of Acholuric Jaundice*

Case	Sex and Age	Anaemia (Hb)	Jaundice	Leg Ulcer	Splenomegaly	Pigment Stones	Family History	Previous Diagnosis
N. M.	F. 48	56%	—	—	Spleen not palpable, but large at operation	—	—	Nil
R. B.	F. 19	62%	Obstructive J. ++	—	Slight	+	+	Obstructive jaundice
J. B.	F. 22	30%	Slight	++	Spleen not large at operation	—	—	Obscure anaemia
M. G. B.	F. 41	74%	—	—	Slight	—	+	P.A.
E. H.	F. 63	40%	Slight	++	+	+	+	P.A.
L. D.	M. 53	56%	Slight	++	+	+	+	Nil
H. A.	M. 52	38%	+	—	Slight	—	+	Nil
W. G.	M. 73	42%	+	—	+	—	—	P.A.
E. R.	F. 68	35%	Slight	+	Slight	—	—	P.A.

unless carried out by someone who has considerable experience of the test, is often valueless and not infrequently misleading. It is not always realized that in a considerable proportion of the cases of F.A.J. the fragility of the red cells is only very slightly increased above the upper limit of normal. In one of our nine cases there was a previous report from a reputable laboratory that the fragility of the red cells was normal; while in another the departure from the normal, though recognized, was so slight that its significance was overlooked. As examples of the variability of the fragility from one case to another the following figures from two of our series are illuminating.

TABLE III.—*Showing Different Degrees of Fragility of Red Cells of Fully Oxygenated Heparinized Venous Blood in 2 Cases of F.A.J. compared with the Normal*

% NaCl	H. A. % Haemolysis	R. B. % Haemolysis	Normal % Haemolysis
0.30	100	100	100
0.35	100	100	100 approx.
0.40	100	100 approx.	60
0.42	100 approx.	—	15
0.44	100 approx.	50	12
0.46	80	20	10
0.48	60	3	Trace
0.50	50	Trace	Nil
0.52	30	Trace	Nil
0.55	20	? Trace	Nil
0.60	10	Nil	Nil
0.65	8	Nil	Nil
0.70	3	Nil	Nil
0.75	Trace	Nil	Nil
0.80	Nil	Nil	Nil

In a satisfactory fragility test it is necessary (1) to make up very accurate solutions of the various saline dilutions; (2) to make certain that the blood is fully oxygenated before introducing it into the saline solutions; and (3) always to carry out a quantitative estimation of the percentage of haemolysis in each saline dilution.

Treatment

From the foregoing description it will be seen that the diagnosis of familial acholuric jaundice, a disease so often unassoci-

(2) Ignorance of the fact that free acid in the gastric juice excludes pernicious anaemia. (3) Failure to appreciate the extreme importance of detailed blood examination. (4) Attribution of natural remissions to the effect of liver administration and of relapses to faulty liver preparations. (5) Failure to grasp the importance of chronic ulceration of the legs and anaemia as signs of familial acholuric jaundice.

SPLenic CYSTS: WITH A REPORT OF A CASE

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Splenic cysts are rare. All writers on this subject begin their articles with these words and go on to quote figures given by Fowler (1940) in analysing 137 cases of non-parasitic splenic cysts.

Andral (quoted by Fowler, 1940) in 1829 described the first splenic cyst, which was found at necropsy and proved to be a dermoid. In 1880 Pean (Fowler, 1940) performed the first splenectomy for a cyst, and in 1906 the first series of 36 cases was described by Powers (Fowler, 1940). Since Fowler's review the interest of surgeons has been aroused, for cases have been recorded in fair numbers. By 1942 McClure and Altemeier had raised the total to 149, and later in that year Gallagher and Mossberger described the 155th non-parasitic cyst. Up to the end of 1944 seven further examples had been listed, and our case would appear, therefore, to be the 163rd.

That the condition is indeed uncommon can be seen by reference to the standard textbooks of surgery and pathology, which have little or nothing to say on the subject. Like most rarities it is of course probable that many cases went unrecorded until more recent years. A search through the literature reveals a willingness on the part of the authors to compose elaborate classifications of these few cases, which discourages us from attempting anything similar.