Discussion

The results of this investigation do not support some of the impressions recorded by Robertson and Leonard. The present results do not exclude the possibility of individual rare syndromes, such as the single cases of "collagen disease" reported by these authors, being caused by T.A.B.T. inoculation.

That unit medical officers were all too ready to ascribe miscellaneous morbid conditions to inoculation was exemplified by occasional cases of traumatic synovitis belonging to the control group being labelled "T.A.B.T. arthropathy." It appeared that many junior medical officers had been warned by their professional seniors of the important aetiological role of T.A.B.T. in what Ogilvie (1954) terms "ephebiatrics."

It should be remembered that T.A.B.T. is usually given at a time when the recruit is adapting himself to a new environment, and that the immediate post-inoculation period is the time when his reaction to "herd life" may be expected to become apparent.

Although the admission of 1% to sick quarters following T.A.B.T. inoculation seems reasonably small at first sight, it can cause considerable administrative embarrassment when large numbers are involved. This admission rate, however, was less than that due to vaccination (1.5%).

Summary

A survey was carried out on 55,459 R.A.F. and W.R.A.F. recruits to determine the morbidity following T.A.B.T. inoculation. The incidence of disease in the test group was significantly lower than that in the controls; nearly all this difference was accounted for by "diseases caused by infection" and persisted in "diseases of the upper respiratory tract."

The admission rate to sick quarters following T.A.B.T. inoculation was 1%, and following smallpox vaccination 1.5%.

No difference in immediate local and general reactions could be detected between subcutaneous and intramuscular T.A.B.T. inoculation.

There was no significant difference between the reactions to T.A.B.T. inoculation classified according to the blood groups of the patients.

T.A.B.T. does not appear to give rise to false-positive Kahn reactions, but vaccination may cause up to 2% false-positive results.

No cases of peripheral neuritis were seen.

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Since the second world war 976 new homes for the aged had been opened in England and Wales, said the Minister of Health, Mr. DEREK WALKER-SMITH, Q.C., when opening an L.C.C. home for the elderly this month. Referring to the size of the problem in Britain, he said that to-day one person in nine was over 65, compared with one in 21 at the beginning of the century. By 1975 this proportion would have risen to one in seven.

MEGALOBlastic ANAEMIA OF INFANCY TREATED WITH FOLIC ACID

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Megaloblastic anaemia in infants was thought to be rare at the McCord Zulu Hospital, Durban, until an incidence of 5.4% was found in 1954 (Walt *et al.*, 1956). Diagnosis was made by bone-marrow examination alone, patients for aspiration being chosen on clinical grounds or when the haemoglobin was below 6.7 g./100 ml. Because that investigation left many questions unanswered a controlled project was initiated. The objectives were to find the true incidence of megaloblastosis; the significance of reticulocytosis; the rapidity with which the bone marrows returned to normal; the part played by antibiotics, particularly penicillin; the cause of the sudden drop in haemoglobin or "crisis" in some patients; and the reasons for the development of megaloblastosis. Answers to some of these questions can now be given.

Although it has been known for a long time that folic acid will cure the megaloblastosis and therefore a deficiency of folic acid is presupposed, we still do not know whether the deficiency is due to lack of intake, absorption, or utilization, nor why it is commonest amongst our cases of kwashiorkor.

Material and Methods

These were similar to those described previously (Walt *et al.*, 1956). To determine the incidence of megaloblastic anaemia in this hospital the bone marrow of every case admitted to the children's wards was aspirated within 24 hours of admission. The series ran from February 14, 1955, to June 5, 1955 (excluding 23 days between March 22 and April 13 because of the Easter vacation), during which time 217 cases were admitted. The bone marrows of 201 cases were examined; of the 16 cases not aspirated, 6 were omitted in error and 10 patients died within a few hours of admission, post-mortem specimens not being obtained.

A further objective was to determine whether the reticulocyte response was a satisfactory measure of effective therapy with folic acid and whether a particular pattern of reticulocyte response could be observed. Two groups of patients were therefore chosen, the first comprising all cases with megaloblastic anaemia and the second consisting of non-megaloblastic cases taken entirely at random; this was done arbitrarily by using every fifth patient admitted as a control case. If the fifth patient suffered from megaloblastic anaemia the next non-megaloblastic case was placed in the control group. This series yielded 18 cases of megaloblastic anaemia and 31 control cases (non-megaloblastic).

The two groups were treated in exactly the same manner, each being given 5 mg. of folic acid three times a day, followed by re-aspiration of the bone marrow within 96 hours. Reticulocyte estimations by the method of Dacie

(1950) were performed three times a week, and haemoglobin levels determined with a Sahli haemoglobinometer twice a week; bone-marrow films were stained with May-Grünwald-Giemsa stain, and all were examined by one of us (S. H.).

The bone marrows were graded into severe, moderately severe, and mild megaloblastic marrow entirely upon the

cytological picture and not on the severity of the primary illness or the degree of anaemia. On the whole we found the sicker child to be more anaemic with a more severely affected marrow, but a fair number of exceptions to this were observed. The bone-marrow grading was as follows:

Severe Megaloblastic Marrow.—Erythropoiesis is very largely or entirely megaloblastic. The predominant cells

TABLE I.—Summary of Cases

No.	Disease	Admission Date (1955)	Age in Months and Sex	Race	Adm Hb (g.%)	Hospital Day of Bone Marrow and Result	Basic Retic. Count (%)	Hospital Day of B.R.C.	Highest Retic. Count (%)	Day of Highest Retic. Count	Normal Bone Marrow Hours After Folic Acid Started	Day Retic. First >11%	Serum Protein			Treatment	Clinical Result
													Total	Alb.	Glob.		
Megaloblastic Anaemia Cases																	
105	Kwkor. Toxic hepatitis	15/2	13 F	A	6.7	Mild 1	6.8	4	6.0	4	72		3.8	1.4	2.4	Pen., Str.	Died (8)
109	Kwkor.	17/2	24 M	A	5.5	Mod. 1	1.6	2	29.8	9	—	7	4.5	2.3	2.2	—	Cured
119	"	21/2	26 F	A	6.7	Mild 1	—	—	15.2	19	79	19	4.3	1.3	3.0	Pen.	Died (3)
122	Kwkor. P.T.B.	21/2	24 F	A	9.7	Mild 1	—	—	Died within 3 days				4.6	1.5	3.1	Str.	
152	Gast. ent.	6/3	5 F	A	7.2	Susp. Mod. 5	4.0	1	15.2	7	70	5	8.0	4.0	4.0	Str., PT	Cured
154	Kwkor.	7/3	34 M	A	7.2	Norm. Mod. 9	8	9	19.4	2	74	2	4.3	1.6	2.7	Pen.	"
167	"	14/3	18 M	A	6.2	Mild 1	2	1	18.4	15	4	4	3.5	1.2	2.3	—	"
169	"	14/3	9 M	A	10.0	Susp. Mild 7	4.8	1	17.8	4	50	4	4.3	2.7	1.6	Pen., Sul.	"
175	Gast. ent.	17/3	2 F	A	7.4	Mild 1	—	—	11.8	24	57	24	4.3	2.7	1.6	—	"
179	Kwkor. B. Pn.	19/3	24 M	A	4.8	Sev. 1	—	—	15.4	7	72	6	3.9	2.5	1.4	Aur., PT	Died (13)
192	Kwkor.	16/4	14 M	A	12.3	Mild 1	0.8	2	6.4	14	No F.A. given	—	4.5	1.9	2.6	—	Died (3)
197	"	19/4	15 F	A	7.3	"	0.4	1	14.8	4	—	4	3.2	1.7	1.5	—	"
234	Kwkor. Tub. adenitis	3/5	24 F	A	6.2	Susp. Mild 3	13.6	1	30.0	12	75	7	5.1	1.6	3.5	Sul., Str., INH	Imp.
254	Kwkor.	16/5	17 M	A	8.9	"	8.4	1	21.0	9	72	5	3.9	1.2	2.7	Pen., PT	"
260	Kwkor. Ot. med.	18/5	16 F	A	9.4	Susp. Mild 5	0.8	1	23.2	15	69	13	4.1	1.6	2.5	Pen.	"
274	"	25/5	21 F	A	9.4	Mod. 1	0.8	1	20.2	21	54	7	6.4	3.0	3.4	Pen., Str.	"
282	Kwkor. Bronchitis	28/5	14 F	A	9.4	"	3.2	1	18.6	19	72	15	4.3	1.6	2.7	Pen., Str.	"
284	Kwkor. Gast. ent.	29/5	8 M	A	7.6	Mild 1	7.2	1	Died within 5 days			Haemolysed				Pen., PT	Died (5)
Control Cases																	
104	Kwkor. Gast. ent. Ot. med.	15/2	20 M	A	7.4	Non-megaloblastic	3	4	3.8	6	96		4.2	2.0	2.2	Pen., Sul., Str., Aur., INH, PT	Died (15)
110	Acute nephritis	17/2	48 F	I	9.2	"	—	—	3.4	21	50		6.4	3.7	2.7	Pen.	Cured
115	Kwkor. Ot. med. Gast. ent.	19/2	14 M	A	6.2	"	—	—	6.4	13	100		3.7	1.3	2.4	"	"
121	B. Pn.	21/2	2 M	A	8.3	"	—	—	7.4	11	104		—	—	—	Pen., Str., PT	"
127	Bac. dys. B. Pn.	24/2	3 M	A	13.6	"	2.2	7	15.0	6	56	6	—	—	—	Pen., Sul., PT	"
132	B. Pn.	27/2	5 F	A	9.1	"	2	2	4	11	90		6.0	2.0	4.0	Pen., Sul.	"
137	Gast. ent. B. Pn.	28/2	1 M	I	12.0	"	0.6	1	—	—	—		—	—	—	Pen., Str., BT	Died (5)
147	"	4/3	11 M	A	3.5	"	5.6	1	—	—	—		7.0	3.5	3.5	"	"
153	Kwkor.	6/3	13 F	A	8.8	"	1.8	1	13.6	17	98	17	4.3	1.6	2.7	Pen.	Cured
164	P.T.B.	12/3	13 M	A	8.8	"	Haemolysed			7.2	3		6.1	3.5	2.6	Str., INH	Imp.
171	Kwkor. Ot. med.	16/3	24 F	A	9.9	"	"	"	9.8	8	50, 70, 168		3.5	1.6	1.9	Pen.	Cured
178	Kwkor. Gast. ent.	19/3	6 F	A	9.4	"	2.8	1	4.2	9	50		6.8	4.2	2.6	Pen., Str., PT	"
184	Kwkor. Bronchitis	21/3	18 M	A	9.4	"	5.8	1	10.2	15	75		3.8	1.9	1.9	Pen.	"
191	Kwkor.	16/4	20 F	A	8.8	"	1	5	15.2	9	54	7	4	1.9	2.1	Pen., Sul., Str.	Imp.
198	Lead poisoning	19/4	15 F	I	"	"	0.8	1	9.8	6	69		6.2	4.3	1.9	Pen., Sul., Str.	"
203	Bac. dys. Ot. med.	22/4	3 M	A	10.6	"	1.6	4	7.8	14	67		4.2	2.8	1.4	Pen., Sul., PT	Cured
208	Gast. ent.	23/4	3 F	A	9.4	"	1	1	6.8	14	68		4.5	3	1.5	Sul., PT	"
214	Kwkor.	26/4	16 M	A	9.4	"	2.2	1	25	22	72	15	3.1	1.2	1.9	Pen., PT	"
220	Osteitis	29/4	36 M	I	"	"	—	—	6	7	68		6.7	4.3	2.4	Pen.	"
225	Bac. dys. B. Pn.	30/4	13 F	A	10.7	"	Haemolysed			5.6	2	57	5.7	3.3	2.4	Pen., Sul., Str., PT	"
230	Burns	2/5	27 F	A	10.7	"	2.8	1	2.4	5	67		6.1	3	3.1	Pen.	"
236	Gast. ent. Ot. med.	6/5	1 F	A	13.4	"	—	—	17.2	9	55	7	5.3	2.2	3.1	Pen., Sul., PT	"
241	Kwkor. Bac. dys.	9/5	20 F	A	10.7	"	—	—	8.2	15	68		3.9	1.8	2.1	Pen., Sul., PT	"
248	Bac. dys.	12/5	8 M	A	8.6	"	5.2	1	11	7	57	7	6.7	4.9	1.8	Aur., P1	"
256	Encephalitis	17/5	16 F	I	10.6	"	0.6	1	4.8	7	55		5.5	2.9	2.6	Pen., Str., INH	"
262	Gast. ent.	20/5	9 M	A	10.7	"	0.4	1	2.2	7	48		9.4	4.1	5.3	Pen., Sul.	"
268	Amoebic dys.	21/5	48 M	A	7.8	"	0.4	2	2	10	55		5.9	2.6	3.3	Pen., Sul., Str.	"
273	Bac. dys.	23/5	6 M	A	10.0	"	4.6	3	9.4	8	72		6.7	3.5	3.2	Pen., Sul., PT	"
281	"	27/5	84 M	A	12.2	"	0.6	1	3.4	3	51		5.1	1.7	3.4	Sul.	"
292	Kwkor. Measles	2/6	16 M	A	10.7	"	1.6	1	6.2	4	77		4.9	2.7	2.2	Pen.	"
297	P.T.B. B. Pn.	3/6	10 M	A	5.4	"	9	6	10.4	2	68		5.3	2.7	2.6	Pen., Str., INH	Imp.

Disease: Kwkor.=Kwashiorkor; Gast. ent.=Gastro-enteritis; Ot. med.=Otitis media; B. Pn.=Bronchopneumonia; Bac. dys.=Bacillary dysentery; P.T.B.=Pulmonary tuberculosis.

Bone-marrow report: Mild=Mild megaloblastic; Mod.=Moderately severe megaloblastic; Sev.=Severe megaloblastic; Norm.=Normoblastic; Susp.=Potential megaloblastic.

Treatment: Pen.=Penicillin; Sul.=Sulphonamides; Aur.=Aureomycin (chlortetracycline); Str.=Streptomycin; INH=Isoniazid; PT=Parenteral fluid therapy; BT=Blood transfusion.

Result: Died (8)=Died on 8th hospital day. Race: A=African; I=Indian.

are primitive very basophilic megaloblasts. Diagnosis is easily made.

Moderately Severe Megaloblastic Marrow.—Erythropoiesis is largely if not entirely megaloblastic; the predominant cell is only a moderately primitive basophilic or polychromatophilic megaloblast. Classical megaloblasts of Ehrlich abound. The diagnosis is extremely easy.

Mildly Megaloblastic Marrow.—Erythropoiesis is only partially megaloblastic, and is frequently predominantly normoblastic. The cells show partial megaloblastic changes and in general are rather mature cells of the polychromatophilic or even the orthochromatic type. Frank megaloblasts may be very scarce or even entirely absent. Diagnosis may be extremely difficult or even impossible.

All cases were given the appropriate treatment for their primary disease (Table I), and for complications where necessary, such as high-protein diets, antibiotics, and parental fluids.

Incidence

Of the 201 patients studied, 18 (9%) had a megaloblastic marrow. Of these, 11 cases were mildly affected, 6 moderately, and 1 severely.

Kwashiorkor was of common occurrence in the megaloblastic series and was present in 16 (89%) of the 18 cases, but in the control group of 31 cases it occurred only 10 times (32%). On the other hand, infection was the predominant feature in only 2 (11%) of the 18 megaloblastic cases, but it occurred in 18 (58%) of the 31 control cases (see Graph). The infections commonly seen

Graph showing number of cases with uncomplicated kwashiorkor, kwashiorkor with infection, and infection alone in both groups.

were bronchopneumonia, gastro-enteritis, otitis media, and bacillary dysentery. An antibiotic or chemotherapy was used in all the control cases and in 13 (72%) of those with megaloblastosis.

Reticulocyte Response

Reticulocyte counts were adequately repeated in 13 cases of megaloblastic anaemia and in 28 controls. All the megaloblastic cases but only six (21%) control cases developed a reticulocyte peak of more than 11% (Table II) after treatment with folic acid. If one accepts the normal reticulocyte count to be less than 5%, then some of the control cases and some of the megaloblastic cases already had a reticulocytosis when admitted (Table III). Three control cases (Nos. 147, 184, and 248) had counts of 5.6%,

TABLE II.—Difference in Reticulocyte Response in the Two Groups

Highest Reticulocyte Count	Megaloblastics		Non-megaloblastics	
	No.	%	No.	%
0-5.5%	0	—	8	28
5.5-11.0%	0	—	14	50
11.0-16.5%	5	38	4	14
16.5-22%	5	38	1	4
22.0-27.5%	3	24	1	4
Total	13		28	

5.8%, and 5.2% respectively, while three megaloblastic cases (Nos. 234, 254, and 284) had counts of 13.6%, 8.4%, and 7.2% on the day of admission (Table I).

TABLE III.—Basic Reticulocyte Counts in First Three Hospital Days in Each Group

Reticulocytes	Megaloblastics		Controls	
	No.	%	No.	%
0-2.8%	6	50	11	65
2.8-5.5%	3	25	4	23
5.5-8.3%	1	8	2	12
8.3-11.0%	1	8	—	—
11.0-13.8%	1	8	—	—
Total	12		17	

Results

Of those with megaloblastosis five died (Cases 105, 122, 175, 179, and 284), two deaths occurring less than 72 hours after admission and the others on the fifth, eighth, and thirteenth hospital day. Their admission haemoglobins were respectively 6.7, 9.7, 7.4, 4.8, and 7.6 g./100 ml. One case (No. 154) had a normoblastic bone marrow on admission, but when re-aspirated nine days later megaloblasts were present. In four other cases (Nos. 152, 169, 234, and 260) the bone marrows did not show true megaloblasts on admission, but the presence of many bizarre myelocytes caused us to repeat the examinations five, seven, three, and five days later respectively, when megaloblasts were found. Three of the control patients died—one in less than 48 hours after admission, one on the fifth day, and one on the fifteenth day. The mortality rate for the controls was 10% and for the megaloblastic anaemia cases 28%.

Discussion

The incidence of megaloblastosis of 9% in this series is appreciably higher than the incidence of 5.4% previously reported (Walt *et al.*, 1956). We feel that this increase can be explained by the use of routine bone-marrow examinations rather than marrow aspirations on clinically suspicious cases only, together with a possible seasonal summer increase, as was suggested in our first investigation (Walt *et al.*, 1956). Some of the additional cases that were detected were probably mild megaloblastic anaemias most of which would have improved spontaneously without folic acid therapy. The relatively high incidence emphasizes once more the value of "a high index of suspicion" for this disease.

Reticulocyte Response

A high reticulocytosis has been accepted as an indication of response to therapy, but the figures have varied with different workers. Their range seemed to be between 4% and 7% (Zuelzer and Rutzky, 1953; Altmann and Murray, 1948), but we had previously found this too low a figure, and in this investigation set out to find an average for our cases. It is well known that a reticulocytosis will result not only from folic acid therapy but secondarily to haemorrhage, a good diet, control of infection, etc., and for this reason the control cases were also given folic acid. Some cases may have had some treatment elsewhere which could have caused a reticulocytosis before being admitted to our wards, but it is very unlikely that this included folic acid; however, we cannot be certain, because the histories are unreliable and parents are not told what treatment is administered. Although this could be the explanation, in other cases counts were not performed until four to five days after admission, when specific treatment (excepting folic acid) had already been started, and in the majority the basic reticulocyte counts were normal (Table III). One control case (No. 297) had a basic reticulocyte count of 9% on the sixth hospital day, while in three cases with megaloblastic changes (Nos. 105, 152, and 154) the reticulocyte counts were 6.8%.

8.6%, and 8.0% on the fourth, fourth, and ninth days respectively. These responses could have been due to the antibiotics administered on admission.

Six control cases developed reticulocyte peaks of over 11%, one occurring on the sixth day after commencing folic acid while others occurred much later—the seventeenth day as in Case 153 (Table I). This patient was suffering from kwashiorkor, had a basic reticulocyte count of 1.8% on the first day, and a normoblastic bone marrow. A high-protein diet, penicillin, and folic acid were begun and the reticulocyte count was followed; it was 5.2% on the third day, 7.4% on the fifth, 1.6% on the seventh, 0.6% on the tenth, 2.4% on the twelfth, 0.6% on the fourteenth, suddenly 13.6% on the seventeenth day, and 11.4% on the nineteenth day. Her illness improved rapidly and she was much better when discharged on the twenty-eighth day.

Similar responses occurred among the cases with megaloblastosis, although on the whole they tended to occur earlier and, of course, had much higher peaks. In three cases (Nos. 119, 154, and 274) "double peaks" occurred, all being more than 11% within the first week after beginning folic acid, returning to normal in the second week, and rising again to over 15% in the third week. These can be explained in Cases 119 and 274, both of which responded to folic acid with a reticulocytosis and a rapid return to normoblastic bone marrows followed by complications with toxæmia, an abscess in one, and pneumonia in the other; both became very ill and needed blood transfusions, and on recovery the reticulocytes rose rapidly again. Case 154, admitted with a normoblastic bone marrow, developed megaloblastosis while on treatment with penicillin and high-protein feeding for kwashiorkor. He responded to folic acid with a 19.6% reticulocytosis, improving clinically, and by the third week had 0.6% reticulocytes; he then relapsed with acute bronchitis and high fever, responded to treatment, and produced 18.4% reticulocytes.

It is obvious that in these cases the assessment of therapy cannot be measured by the reticulocyte response, which is irregular and unreliable and not at all as clear-cut and uniform as in pernicious anaemia. This is in direct contrast to the findings of Gerbasi (1953), who states that the reticulocyte crisis begins 48 hours after the commencement of treatment and is maximal on the fourth day.

Bone-marrow Response

Because our diagnosis was usually made by bone-marrow estimation we felt that the best test of cure of the megaloblastosis would be a rapid return to a normoblastic pattern, and in 15 cases the bone marrows were re-examined within 96 hours of starting therapy with folic acid, and all were found to be normoblastic; in 11 cases the bone marrow was normoblastic within 79 hours of therapy.

Haemoglobin Levels

Megaloblastosis was usually associated with an anaemia, but this was not invariable, and when present the anaemia was not necessarily severe. We feel, however, that, as the presence of megaloblasts in the bone marrow is likely to lead to a serious and alarming anaemia at any time, megaloblastic anaemia should be seriously considered in any child with a haemoglobin below 6.7 g./100 ml. as reported earlier (Walt *et al.*, 1956), and a bone-marrow aspiration performed immediately.

Aetiology

Megaloblastic anaemia of infancy (Adams, 1954) and of pregnancy (Adams and Wilmot, 1953) is apparently much more common in Durban than elsewhere in South Africa. Very few cases have been discovered in Johannesburg (Altmann and Murray, 1948) and Capetown (J. F. Brock, personal communication). We cannot account for this, because the diets of the lowest-income groups in these three large centres are probably very similar.

In Italy both Amato (1946) and Gerbasi (1950) have described many cases of megaloblastic anaemia in infants, and

more recently Gerbasi and Burgio (1955) have described it in children with a disease apparently very similar to our cases of kwashiorkor. In our patients infections with tropical diseases such as hookworm, roundworm, and *Entamoeba histolytica* are not heavy and cannot be the sole cause of megaloblastosis, but many of our cases have a large number of leucocytes in the stools, and bacillary dysentery may possibly play an important part. In most cases cultures of stools did not reveal any specific pathogenic organism, but, unfortunately, repeated cultures could not be made.

Many of our cases of kwashiorkor are associated with megaloblastosis, and protein deficiency is obviously an important aetiological factor. The diarrhoea so often associated with it may prevent the absorption of folic acid. The cause cannot be protein lack alone, because some of our cases of kwashiorkor showed only suspicious bone marrows on admission, and despite a high-protein diet of lactified skimmed milk, which we know cures kwashiorkor, they went on to develop typical megaloblasts in the bone marrow. Some other factors must also play a part, because routine bone-marrow examinations revealed more mild cases than were suspected clinically. We believe that some patients develop a mild megaloblastosis which disappears spontaneously when the kwashiorkor improves or as soon as the infection disappears, or when the diarrhoea stops, and that these cases are never diagnosed clinically.

It is possible that vitamin B₁₂ is also necessary in conjunction with high-protein feeding. May *et al.* (1952), on the other hand, have shown that in monkeys the toxæmia from an abscess produced by the injection of turpentine will cause a megaloblastosis of the bone marrow. We feel, too, that infection plays an important part in some cases, but we have not been impressed by the bone-marrow response to penicillin or chemotherapy. Foy *et al.* (1950) thought that the megaloblastosis might be related to protein deficiency, but later they reported, in separate articles (Foy *et al.*, 1951a, 1951b), two cases which responded to penicillin alone. Many of our cases were given antibiotics because of some superimposed infection, and, despite this, they developed megaloblastosis. Others again did not improve until folic acid therapy had been instituted.

Summary

During a controlled study of megaloblastic anaemia in infancy an incidence of 9% was found in 201 cases admitted over a period of three months, during which time routine bone-marrow examinations were made on all admissions.

Of the cases with megaloblastic anaemia 89% had kwashiorkor.

All cases showed reticulocyte peaks of over 11%, but reticulocytosis occurred at variable times and in no set pattern, and could not be used as a test of cure.

The bone marrows became normoblastic within 96 hours of beginning folic acid therapy. Despite this the haemoglobin levels did not rise rapidly.

The aetiology is not known, but protein deficiency, dysentery, and other infections probably play the major part.

Because megaloblastosis is so commonly associated with kwashiorkor it is recommended that all cases of kwashiorkor should be given folic acid for three weeks.

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MEDULLARY APLASIA IN CHRONIC MYELOID LEUKAEMIA DURING BUSULPHAN THERAPY

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Busulphan (1:4-dimethanesulphonyloxybutane; "myleran") is now well established as an effective and relatively safe agent in the control of chronic myeloid leukaemia. Haddow and Timmis (1953) first noted the strong depressant action exerted by this compound on myelopoiesis, and many clinical trials in leukaemic and neoplastic states have since been reported (Galton, 1953; Bollag, 1953; Wilkinson, 1953; Hansen, 1954; Wagner, 1954; Petrakis *et al.*, 1954; Galton and Till, 1955; Haut *et al.*, 1955; Bernard *et al.*, 1955; Kurrle, 1955; Louis *et al.*, 1956; Blackburn *et al.*, 1956; Frost and Jackson, 1956; Greig, 1956; Hyman and Gellhorn, 1956). From the results of these trials it is clear that busulphan has a remarkably specific action against the myeloid cell series, and is capable of bringing into good remission over 80% of patients suffering from chronic myeloid leukaemia. It is inactive in acute leukaemia, in chronic lymphatic leukaemia, and in neoplastic conditions, including the lymphomas.

Patients treated with busulphan are singularly free from the unpleasant side-effects which would result from simultaneous attack on rapidly dividing normal tissues, such as the skin or the gastro-intestinal mucosa. Only two important toxic reactions have been recorded in the considerable literature that has now accumulated on busulphan therapy in chronic myeloid leukaemia. One is a progressive myeloid depression—an exaggeration of the desired therapeutic response—leading to marrow aplasia. The other is renal failure due to hyperuricaemia caused by very rapid breakdown of granulocytes. It would be misleading to give the impression that either of these two reactions occurs often, but, despite their rarity, both are serious enough to warrant close attention, particularly when suggestions for the routine use of busulphan are being put forward and the drug is being increasingly prescribed by general physicians. The development of hyperuricaemia can be avoided, as Hyman and Gellhorn (1956) suggest, by adjusting dosage to prevent too sharp a fall in leucocyte count, and by

forcing fluid intake to 3 to 4 litres daily during the danger period. It would also seem reasonable to maintain an alkaline urine. In our own restricted experience of 12 cases this problem has not arisen, but we have encountered two cases of marrow aplasia while using dosages within a range generally regarded as orthodox.

In the present report we give details of the toxic reactions in these two patients, and make some general observations on precautions in the routine use of busulphan.

Case 1

A woman aged 30 was admitted to hospital in February, 1955, having complained of abdominal swelling for six months, frequency of micturition and dysuria irregularly for four months, and aching in legs and back and nocturnal sweating for two months. She was found to have massive enlargement of the spleen, which extended across the midline and 25 cm. below the xiphisternum. The blood count showed a typical picture of chronic myeloid leukaemia, with haemoglobin 9 g. per 100 ml. and total leucocytes 700,000 per c.mm., with 300,000 granulocyte precursors per c.mm. She was treated with mercaptopurine, and an initial course of 150 mg. daily was given for 18 days. After an interval of a month, a second course of this drug was given for seven days. The effect of this treatment on the peripheral blood count is shown in Fig. 1; the leucocyte and platelet counts showed on each of the two occasions a response during the period of administration, with continued increasing effect for about two weeks after the drug was stopped, and then rapid relapse.

Because of the erratic response to mercaptopurine, busulphan was started on April 14 at a dosage of 4 mg. daily. After 72 days on this dose the response with respect to the haemoglobin level, leucocyte count, splenomegaly, and general clinical state was unimpressive, and the dose was increased to 10 mg. daily for the next 28 days. The response was dramatic, the haemoglobin rose steadily from 9.9 to 12.6 g. per 100 ml., the leucocytes fell from 230,000 to 70,000 per c.mm., and the spleen was greatly reduced in size. The dose was then decreased to 8 mg. daily and treatment continued for 58 days. By that time the patient had become symptom-free, the spleen tip could only just be felt on deep inspiration, the haemoglobin level was 12.4 g. per 100 ml., the leucocytes numbered 6,000 per c.mm. with a normal differential count, and the platelet count was 200,000 per c.mm. Because the response to the initial daily dose of 4 mg. of busulphan had been slight a maintenance dose of 4 mg. daily was then started.

FIG. 1.—Case 1. Haematological response to treatment.