

## Vitamin B<sub>12</sub> absorption after necrotizing enterocolitis

J E COLLINS, C J ROLLES, H SUTTON, AND D ACKERY

*Departments of Paediatrics and Nuclear Medicine, Southampton General Hospital, Southampton*

**SUMMARY** Resection of the terminal ileum for necrotizing enterocolitis is not uncommon in neonates requiring intensive care in the first weeks of life. They may therefore be at risk of vitamin B<sub>12</sub> malabsorption, and later of vitamin B<sub>12</sub> deficiency. A method of measuring B<sub>12</sub> absorption is described and the results are given. This assessment should be part of the follow up for all these children.

Great advances have been made in the care of sick, preterm infants. With better control of their respiratory disorders, gastrointestinal and nutritional problems have become relatively more important in determining ultimate prognosis. Neonatal necrotizing enterocolitis is now a common disorder, and if surgery proves necessary the terminal ileum is the most common site of resection. Although much of the intestine has the ability to adapt its function after surgery, this does not occur for absorption of vitamin B<sub>12</sub>, which is dependent on the presence of specific receptor sites. These receptor sites are situated in the terminal ileum with their greatest activity close to the ileocaecal valve. If a critical length of terminal ileum is resected inadequate vitamin B<sub>12</sub> absorption will occur and when hepatic stores have been exhausted some years later, vitamin B<sub>12</sub> deficiency will follow.<sup>1</sup>

The developing brain seems to be more susceptible to vitamin B<sub>12</sub> deficiency than the developed one. Not only may children suffer megaloblastic anaemia but also neurological problems including paraesthesiae, involuntary movements, and importantly, developmental delay.<sup>2-5</sup> There is no satisfactory clinical method of determining which children who have undergone resection of their terminal ileum for necrotizing enterocolitis are at risk of vitamin B<sub>12</sub> deficiency. Symptoms and signs may not show for some years after the child has been discharged from the hospital's care;<sup>6</sup> vitamin B<sub>12</sub> absorption should be assessed before this occurs.

### Patients and methods

Fourteen children aged 1 to 7 years who had undergone ileal resection for necrotizing enterocolitis were studied. Further details are given in the Table. All had been born between 27 and 34 weeks'

gestation. Estimates of the length of ileum resected were made from operative diagrams, measurements by the surgeon, and measurements of fixed specimens by the pathologist. None of the children had ever been considered to need B<sub>12</sub> supplements.

Vitamin B<sub>12</sub> absorption was assessed by a whole body counting method using the Shadow Shield whole body counter. After assessment of the background count an oral dose of 0.25 µg <sup>58</sup>Co labelled vitamin B<sub>12</sub> was given, and the count repeated. Five of the 14 children tolerated this procedure only if their mother was present during the counts. The dose of labelled vitamin B<sub>12</sub> is lower than in previous work<sup>7</sup> but was found to give adequate counts when using this equipment. It was freshly mixed with a drink of the child's choice which also contained 150 mg of carmine red. The carmine was used as a stool marker to assess mouth to anus transit time.<sup>8</sup> All children had their normal bowel habit on the day of the test. The mother was asked to note when the child's stools first showed red. A normal child in this age range passes the marker after about 24 to 48 hours.<sup>9</sup> Blood was taken for a full blood count and serum vitamin B<sub>12</sub> estimation.

A week later the child returned for a repeat count. The percentage of the dose retained was calculated. A normal adult absorbs at least 45% of the dose.<sup>1</sup> For ethical reasons no normal children were studied.

### Results

The results are given in the Table. All the children had normal full blood counts and serum vitamin B<sub>12</sub> concentrations at the time of the study. Estimates made by the surgeon and pathologist of the length of terminal ileum resected varied considerably, and in some cases no estimate of the length of the resection

Table Details of 14 children who underwent ileal resection for necrotizing enterocolitis grouped according to whether their vitamin B<sub>12</sub> absorption was greater than 45% or 45% and less

Case No	Age (years)	Haemoglobin (g/dl)	Serum vitamin B <sub>12</sub> * (µg/l)	Mother present at testing <sup>†</sup>	Ileum resected (cm)		Ileocaecal valve removed	Gut transit time (hrs)	% vitamin B <sub>12</sub> absorbed
					Surgeons' estimate	Pathologists' estimate			
<i>Vitamin B<sub>12</sub> absorption &gt; 45%</i>									
1	2	13.4	384	-	—	3.5	Yes	48	96
2	5	12.3	862	-	10	14	No	96	94
3	4	11.8	1000	-	15	10	No	56	87
4	5	13.3	921	-	2	—	No	70	87
5	2	11.4	445	-	5	—	Yes	60	81
6	1	12.0	770	+	8	8	Yes	7	73
7	2	12.4	1000	+	6	15	Yes	54	63
8	7	13.1	422	-	16	14	Yes	48	53
<i>Vitamin B<sub>12</sub> absorption ≤ 45%</i>									
9	3	12.6	320	-	3	7	Yes	8	45
10	3	12.3	728	+	—	46	Yes	3	34.5
11	4	12.6	460	+	45	—	Yes	3	32
12	2	13.0	315	-	20	12	Yes	4	26
13	1	11.4	900	-	15	15	Yes	4	21
14	3	11.8	218	+	—	34	Yes	4	11

\*Normal range 150–1000 ng/l.

<sup>†</sup>Child and mother going through the tunnel of the whole body counter together.

was made. Only three of the 14 children had an intact ileocaecal valve (cases 2, 3, and 4).

Six of the 14 children had abnormal vitamin B<sub>12</sub> absorption of less than 45% (see Table). None of the children with an intact ileocaecal valve had vitamin B<sub>12</sub> malabsorption. The presence of the mother during the test had a negligible effect on the percentage absorbed, indicating that body attenuation did not affect the count. Two children, cases 6 and 13, were studied with and without the mother being present—the former showed normal absorption and the latter abnormal absorption on both occasions.

The children could also be divided into two groups depending on their total gut transit time—one group with a transit time of less than 12 hours and a second with a transit time greater than 24 hours (see Table). Seven children had a gut transit time of less than 12 hours. All three of the children with an intact ileocaecal valve had a normal transit time.

There is a clear association between total gut transit time and the percentage absorption of vitamin B<sub>12</sub> (Figure (a)). Those children with a fast gut transit time (that is less than 12 hours) are likely to have vitamin B<sub>12</sub> malabsorption. Only one child with a transit time of less than 12 hours had normal

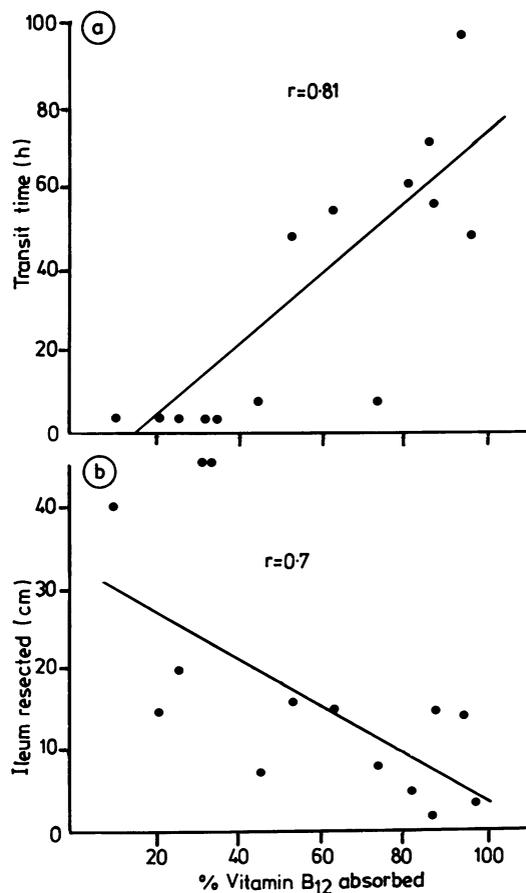


Figure Relation between (a) total gut transit time and (b) length of ileum resected and percentage absorption of vitamin B<sub>12</sub> in 14 children who had undergone ileal resection for necrotizing enterocolitis.

vitamin B<sub>12</sub> absorption. There is also an association between the length of ileum resected and the percentage of vitamin B<sub>12</sub> absorbed (Figure (b)). This shows a trend rather than a clear cut linear relation. Scatter is so great that it would not be helpful in an individual patient. If greater than 20 cm of terminal ileum has been resected, vitamin B<sub>12</sub> malabsorption is likely, although one child (case 13) had only 15 cm resected and showed abnormal absorption of only 21%. This child had the ileum just proximal to the ileocaecal valve removed and this is the area of maximal receptor site activity.

### Discussion

Children who have undergone resection of the terminal ileum for necrotizing enterocolitis are at risk of vitamin B<sub>12</sub> malabsorption because specific receptor sites for the absorption of the vitamin B<sub>12</sub> intrinsic factor complex are found only in the terminal ileum.<sup>1</sup> Only a small percentage of vitamin B<sub>12</sub> diffuses passively across the bowel wall.<sup>10</sup> Because symptoms and signs of deficiency take some years to develop the need for vitamin B<sub>12</sub> supplements may be forgotten. Accurate assessment of each child's need for supplements should be part of their routine follow up.

This method of determining vitamin B<sub>12</sub> absorption is simple and accurate. A standard Schilling test is an alternative but the incomplete collection of urine is a serious source of error.<sup>10</sup> It is notoriously difficult to perform 24 hour urine collections on infants or small children. The whole body counting method is based on that used by Valman,<sup>7</sup> with some modifications. Food does not interfere with vitamin B<sub>12</sub> absorption and therefore fasting is unnecessary.<sup>11</sup> The presence of the mother during the test does not seem to alter the result significantly. The children studied here showed a spectrum of absorption from 11 to 96%. Both in this study and previous studies<sup>7</sup> children with relatively short ileal resections seemed to absorb more than 45% of the vitamin B<sub>12</sub> and therefore, at present, it seems reasonable to accept the same lower limit for children and adults. Only long term follow up will determine which value will eventually lead to deficiency (which is what matters), but we recommend that lifelong vitamin B<sub>12</sub> supplements be given to children with absorption of 45% or less. The alternative would be to monitor blood concentrations regularly.

The association between low vitamin B<sub>12</sub> absorption and fast total gut transit time is of interest. All children with absorption of 45% or less have an abnormally fast mouth to anus transit time. Carmine red was used to measure this as it is simple and safe,

and results seem to be reproducible.<sup>8 12</sup> There are more sophisticated methods of determining gut transit time using radio-opaque markers but their use was not considered to be justified here.<sup>13</sup> Mouth to anus transit time is dependent on the presence of the ileocaecal valve. There is experimental evidence showing that an intact ileocaecal valve prolongs transit time in the small bowel, and therefore total transit time.<sup>14</sup> This hold up of gut contents in the small bowel allows more efficient vitamin B<sub>12</sub> absorption at the receptor sites. Absence of the valve also allows colonic bacteria to colonise the small bowel and these compete with the available vitamin B<sub>12</sub> receptor sites for the vitamin B<sub>12</sub> and intrinsic factor complex.<sup>3 15</sup> The three children with an intact ileocaecal valve have normal gut transit times and normal vitamin B<sub>12</sub> absorption.

The length of terminal ileum resected seems to be little more than a general guide to those children likely to suffer from vitamin B<sub>12</sub> malabsorption. Although ileal resection of greater than 20 cm puts a child at definite risk, one child who had only 15 cm of terminal ileum removed has particularly abnormal vitamin B<sub>12</sub> absorption. Obviously it is dependent on a critical number of receptor sites being removed and therefore a child with a resection just proximal to the ileocaecal valve is especially at risk.

In conclusion, although more data are needed, it is clear that some children who have had surgery for necrotizing enterocolitis do not absorb vitamin B<sub>12</sub> properly and deficiency will develop if they are not given supplements. Over one third of the patients we studied show appreciable vitamin B<sub>12</sub> malabsorption, although at the time of surgery the length of resection was not considered likely to produce this. Children with fast gut transit times seem particularly at risk because they are likely to have had their ileocaecal valves removed.

All children who have had any terminal ileum resected for necrotizing enterocolitis, especially if the ileocaecal valve has been removed, should have their vitamin B<sub>12</sub> absorption checked.

We thank Dr P J Milla for advice and encouragement during preparation of this paper.

### References

- 1 Chanarin I. *The megaloblastic anaemias*. 2nd ed. Oxford: Blackwell, 1979.
- 2 Rodgers BM, Talbert JL, Moazam F, Felman AH. Functional and metabolic evaluation of colon replacement of the oesophagus in children. *J Pediatr Surg* 1978;13:35-9.
- 3 Dallman PR, Diamond LK. Vitamin B<sub>12</sub> deficiency associated with disease of the small intestine. *J Pediatr* 1960;57:689-94.
- 4 Clark ACL, Booth CC. Deficiency of vitamin B<sub>12</sub> after extensive resection of the distal small intestine in an infant. *Arch Dis Child* 1960;35:595-9.

- <sup>5</sup> Wighton MC, Manson JI, Speed I, Robertson E, Chapman E. Brain damage in infancy and dietary vitamin B<sub>12</sub> deficiency. *Med J Aust* 1979;**14**:1-3.
- <sup>6</sup> Valman HB. Late vitamin B<sub>12</sub> deficiency following resection of the ileum in the neonatal period. *Acta Paediatr Scand* 1972;**61**:561-4.
- <sup>7</sup> Valman HB, Roberts PD. Vitamin B<sub>12</sub> absorption after resection of ileum in childhood. *Arch Dis Child* 1974;**49**:932-5.
- <sup>8</sup> Dimson SB. Carmine as an index of transit time in children with simple constipation. *Arch Dis Child* 1970;**45**:232-5.
- <sup>9</sup> Wolman IJ. *Laboratory applications in clinical paediatrics*. New York: McGraw Hill, 1957:696.
- <sup>10</sup> Smith CH. *Smith's blood diseases of infancy and childhood*. 4th ed. Miller DR, ed. St Louis: C V Mosby Company, 1978.
- <sup>11</sup> Tait CE, Hesp R. Measurement of <sup>57</sup>Co-vitamin B<sub>12</sub> uptake using a static whole body counter. *Br J Radiol* 1976;**49**:948-50.
- <sup>12</sup> Dimson SB. Transit time related to clinical findings in children with recurrent abdominal pain. *Pediatrics* 1976;**47**:666-74.
- <sup>13</sup> Haddad H, Deuroede-Bertrund G. Large bowel motility disorders. *Med Clin North Am* 1981;**65**(b):1388.
- <sup>14</sup> Gazet JC, Kopp J. Surgical significance of the ileo-caecal junction. *Surgery* 1964;**56**:565-73.
- <sup>15</sup> Weser E. Nutritional aspects of malabsorption. Short gut adaptation. *Am J Med* 1979;**67**:1014-20.

Correspondence to Dr Jane Collins, Department of Child Health, Institute of Child Health, Guilford Street, London WC1.

Received 5 March 1984