Nicholson[7] reported that rebound insomnia is uncommon even after administration of hypnotics with short lives, and we question the relevance of this phenomenon.

We accept that the results of the present study are based on rather subjective data and that we did not measure the period of rapid eye movement, obtain electroencephalograms, or assess any other objective neurophysiological indices. Nevertheless, many of the same questions were asked in different ways. Hence the additional questions "Did the treatment help you sleep?" and "How long did you sleep?" provided results that were exactly the same as those elicited by the questions "Were you satisfied with the night's sleep?" and "How did the length of sleep compare with usual?"

Remarkably few studies have been carried out on the value of single-dose hypnotic treatment for patients before major and minor operations, although two studies have suggested that hypnotics improve the duration and quality of sleep before operation.[8 9] The results of the present study leave us in no doubt that triazolam is safe and effective for patients before elective operation.

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(*Accepted 12 August 1980*)

Effect of bile on vitamin B_{12} absorption

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Summary and conclusions

The standard double-isotope Schilling test was used to study vitamin B_{12} absorption in seven patients with obstructive jaundice and 10 with T-tube bile duct drainage after cholecystectomy and bile duct exploration. In three and five of these patients respectively absorption was impaired. In the second group six patients were restudied after removal of the T tube, and in each case absorption was improved. Similar results were obtained after bile duct ligation in rats. Bile exclusion produced a 50-60% reduction in renal and hepatic uptake of vitamin B_{12} from the intestinal lumen. The malabsorption was corrected by replacing bile.

These studies suggest that bile plays a part in the normal absorption of vitamin B_{12}.

Introduction

In man both vitamin B_{12} and bile acids are absorbed in the ileum[1 2] but the relation between these processes has not been defined. We have therefore tried to determine whether bile acids play a part in the absorption of vitamin B_{12}.

Materials and methods

Human studies—A standard double-isotope Schilling test was performed on seven patients with obstructive jaundice and 10 patients with T-tube drainage of the common bile duct for biliary calculi. The project was approved by the hospital ethics committee and informed consent obtained from all patients. After an overnight fast patients swallowed capsules containing ^{57}Co-vitamin B_{12} bound to intrinsic factor and ^{58}Co-vitamin B_{12}; non-radioactive vitamin B_{12} (1 mg) was given intramuscularly at the same time. The fast was maintained for a further two hours and the urine output collected for 24 hours. Absorption of vitamin B_{12} was expressed as the percentage of the oral dose excreted in the urine over 24 hours. In a patient with carcinoma of the common bile duct (case 7) the test was repeated with oral chenodeoxycholic acid 250 mg given hourly for the first three hours. In the patients with T-tube drainage the test was done between the fifth and seventh postoperative days with the T-tube still in situ. In six patients the test was repeated, in three (cases 8, 10, and 17) within a week and in the other three (cases 11-13) one month after the tube had been removed.

Rat experiments—Vitamin B_{12} absorption was studied in three groups of eight female albino Wistar rats weighing 150-200 g. A sham operation was performed on the animals in group 1 and the bile duct ligated in groups 2 and 3. On the day after operation each animal was given 0·005 μg ^{57}Co-cyanocobalamin in 0·2 ml physiological saline directly into the stomach. One and three hours later 1 ml rat bile was infused into the stomach of the animals in group 3. All animals were killed at seven hours. At the end of the experiment the kidneys, liver, stomach, colon, and small intestine were removed. The small intestine was divided into three segments, the lumen of each flushed with 15 ml deionised water, and the washings collected. The radioactivity of the organs and intestinal contents were counted in a Packard gamma counter.

Results

Human studies—Of the patients with obstructive jaundice (table I), the three with carcinoma of the head of the pancreas had severe cholestasis, plasma bilirubin concentrations exceeding 170 μmol/l (9·9 mg/100 ml). Absorption of vitamin B_{12} was abnormal in two of these patients and at the lower limit of normal in one. The patient with carcinoma of the common bile duct had abnormal absorption, and at operation his pancreatic duct was noted to be normal. When the Schilling test was repeated with 750 mg chenodeoxycholic acid his urinary excretion of ^{57}Co-vitamin B_{12} and ^{58}Co-vitamin B_{12} improved

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from 6·2% to 13·4% and from 6·4% to 14·3% respectively. The patients with primary biliary cirrhosis had a milder degree of cholestasis, and the absorption was normal in two and at the lower limit of normal in one. Of the patients with T-tube bile duct drainage (table II), five showed abnormal absorption of vitamin B_{12}. In each of the six patients retested after removal of the T-tube the absorption was improved ($p < 0·001$). The result was similar whether the test was repeated within a week or a month after the T-tube had been removed.

Rat experiments—The figure shows the distribution of ^{57}Co-vitamin B_{12} in the gut lumen and organs of the rats. In all groups over 95% of the radioactivity in the gut lumen had passed the middle segment of the small intestine, which is the maximal absorptive site for vitamin B_{12}.[3 4] In groups 2 and 3 the pattern was the same, indicating that the transit time was similar. The mean liver uptakes in groups 1, 2, and 3 were 4·4±SEM 0·25%, 2·0±0·39%, and 4·3±0·43% respectively; kidney uptakes were 10·1±0·50%, 4·4±1·42%, and 11·7±0·69%; and small-intestinal and colonic contents were 34·9±4·39%, 49·1±20·77%, and 24·9±3·74%. The uptake of ^{57}Co-vitamin B_{12} by the liver and kidneys was significantly lower in group 2 than in groups 1 ($p < 0·005$) and 3 ($p < 0·005$), and the radioactivity in the small-intestinal and colonic contents was significantly higher in group 2 than in group 3 ($p < 0·05$).

Discussion

Apart from the secretion of intrinsic factor, several gastrointestinal processes play a part in the absorption of vitamin B_{12}. These include the acid-pepsin digestion of vitamin B_{12} present in food[5]; the pancreatic protease digestion of R protein, which would otherwise sequestrate vitamin B_{12} from absorption[6]; and the concentration of divalent cations in the intestinal lumen.[7] There is also evidence that bile may influence the absorption of vitamin B_{12}. Impaired absorption of vitamin B_{12} was observed in patients with obstructive jaundice in whom both the bile duct and the pancreatic duct were obstructed.[8] Our results in patients with obstructive jaundice were similar. We also found that in a patient with bile duct occlusion in the absence of pancreatic duct disease the absorption of vitamin B_{12} was impaired. When the Schilling test was repeated along with chenodeoxycholic acid supplements absorption more than doubled.

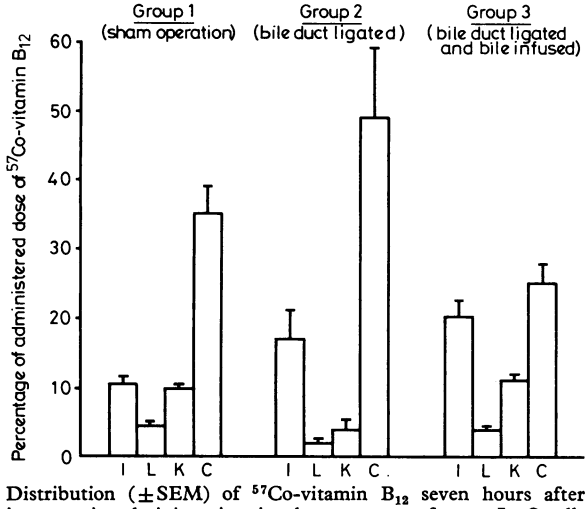
We observed impaired absorption of vitamin B_{12} in patients with T-tube common bile duct drainage. Restoring normal bile flow in these patients produced a significant increase in absorption. Possibly the initial impaired absorption reflected the effect of the operation on intestinal function. Nevertheless, the increased absorption occurred irrespective of the interval between the initial and repeat Schilling tests, which suggests that the improvement was not due to postoperative changes. Furthermore, vitamin B_{12} absorption tested within a week of appendicectomy has been found not to be impaired (unpublished observation). The amount of bile diverted by the T tube was variable and was in general less than the total daily output estimated.[9] Hence an optimum quantity of bile is apparently necessary to maintain the absorption of vitamin B_{12} at its normal level.

A similar effect on the absorption of vitamin B_{12} was observed in the rat experiments when bile was excluded from the intestine (figure). Bile duct ligation with undisturbed pancreatic ducts and

TABLE I—*Vitamin B_{12} absorption in patients with obstructive jaundice*

Case No	Diagnosis	Age and sex	Plasma bilirubin concentration (normal value 3-4 μmol/l)	Schilling test result ^{57}Co-vitamin B_{12} (normal 12-30%)	Schilling test result ^{58}Co-vitamin B_{12} (normal 11-28%)
1	Primary biliary cirrhosis	57F	47	26·4	27·5
2		51F	38	17·9	17·6
3		67F	158	12·6	13·5
4	Carcinoma of head of pancreas	49M	>170	13·4	13·0
5		59F	>170	6·6	6·4
6		66M	>170	3·0	3·3
7	Carcinoma of common bile duct	56M	>170	6·2	6·4

Conversion: SI to traditional units—Bilirubin: 1 μmol/l ≈ 0·06 mg/100 ml.



Distribution (±SEM) of ^{57}Co-vitamin B_{12} seven hours after intragastric administration in three groups of rats. I=Small-intestinal wall. L=Liver. K=Kidneys. C=Small-intestinal and colonic contents.
Unpaired Student's *t* test: group 2 L+K *v* groups 1 and 3 L+K $p < 0·005$; group 2 C *v* group 3 C $p < 0·05$.

TABLE II—*Vitamin B_{12} absorption in patients with T-tube bile duct drainage*

Case No	Diagnosis	Age and sex	Bile volume in 24 hours (ml)	Schilling test result (%) T tube in situ ^{57}Co-vitamin B_{12}	T tube in situ ^{58}Co-vitamin B_{12}	T tube removed* ^{57}Co-vitamin B_{12}	T tube removed* ^{58}Co-vitamin B_{12}
8	Cholelithiasis	59F	300	4·3	4·8	15·1	16·5
9	,,	21F	350	5·7	7·6		
10	,,	61M	550	6·5	7·5	8·8	9·2
11	,,	60M	225	9·8	10·1	14·0	15·0
12	,,	48F	250	8·9	8·9	22·0	25·0
13	,,	70F	400	12·8	12·6	23·9	22·9
14	,,	45M	250	13·9	21·3		
15	,,	54F	400	16·6	17·5		
16	,,	74M	1030	17·0	21·6		
17	,,	24F	200	22·4	23·4	31·0	28·0

*Statistical analysis by paired Student's *t* test: $p < 0·001$ compared with T tube in situ.

similar intestinal transit times impaired the absorption of vitamin B_{12} when compared with the control rats. As a result the liver and kidney uptake of radioactive vitamin B_{12} was reduced, and correspondingly there was more vitamin B_{12} retained in the gut lumen. This malabsorption was completely corrected when bile was replaced. These results confirm that bile influences[10] and enhances the absorption of vitamin B_{12} in rats. The mechanism by which bile enhances the absorption of vitamin B_{12} is unknown. Although intestinal pH[11] and calcium ion concentration[7] influence the uptake of vitamin B_{12} by the ileal mucosa, these factors are probably not relevant to the effect of bile as described.

Bile contains minimal quantities of bicarbonate when compared with pancreatic juice, and its calcium content is not greater than that in gastric or pancreatic juice.[12] On the other hand, bile and bile acids interact with intrinsic factor and intrinsic factor-vitamin B_{12} in vitro. In particular, dihydroxy bile acids inhibit the binding of vitamin B_{12} to intrinsic factor,[13] while conjugated trihydroxy bile acids dissociate vitamin B_{12} from the intrinsic factor-vitamin B_{12} complex.[14] These in-vitro interactions may be physiologically important. Vitamin B_{12} is normally bound to both intrinsic factor and R protein in equal proportions in the stomach. The vitamin B_{12} bound to R protein is subsequently transferred to free intrinsic factor when R protein is degraded by the pancreatic enzymes in the upper intestine.[6 15] Indeed, impairment of this degradation process has been proposed as the cause of malabsorption of vitamin B_{12} in pancreatic insufficiency.[15] Furthermore, the presence of excess free intrinsic factor reportedly inhibits the attachment of intrinsic factor-vitamin B_{12} to ileal mucosa.[16] Possibly the binding of bile acids to free intrinsic factor in the upper intestine prevents the inhibition which would otherwise occur. Alternatively bile acids may dissociate the intrinsic factor-vitamin B_{12} complex at the specific receptor site, thus enhancing the absorption of vitamin B_{12}.

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(*Accepted 12 August 1980*)

ONE HUNDRED YEARS AGO Sir,—The tradesman, who, whilst vending an inferior article at a first-class price, holds out to the public a bait in the shape of a trumpery "present," is of course looked upon by all his fellows (who would be honest if they were allowed) as a mean underhanded person, who seeks to enrich himself by any means, however sordid, at the expense not only of his brethren, but of the public generally, and one who aims at the very root of all fair dealing. But what shall we think of a member of a learned profession, who, instead of trying to raise the status of his calling, degrades not only himself, but his brother practitioners, by such mean and paltry acts as advertising, puffing, and, without a blush of shame, offers his services at so many pence? I have not the honour legally to belong to your profession, inasmuch as I am unqualified, and have nothing to look forward to but a life of hard work as an assistant. Still, I consider my position far preferable to that of a man whose windows are plastered over with whitening like those of a mock auction room, and daubed with a dozen such inscriptions in red and blue, as "Certificates for Clubs and Schools, 6d. each," "Visits, 6d. each," "Advice and Medicine, 6d. *each bottle*" (*sic*), etc. So long as I uphold the honour of my profession by all means in my power, by conducting the practice of my principal in a gentlemanly manner, having a due regard for all the little amenities of medical etiquette, and so long as I continue to look upon the means by which I earn my living as one of the noblest on God's earth, so long shall I think myself socially and professionally the superior of a "qualified gentleman," who stands on his doorstep of an evening in his shirt-sleeves, smoking a long pipe. I often wonder if the turning over in his pockets of the money obtained in so mean and grovelling a manner is sufficient to compensate him for the contempt of, not only his professional brethren, but even of their "unqualified" assistants. I enclose two handbills emanating from the surgery of this "gentleman," in which, like Little Jack Horner, he proclaims to the public, "What a great man am I!" And of what class are his assistants, Drs —— and ——? have they taken service in such a concern knowing it to be what it is? If they are, as their principal "advertises" them, two qualified men, then have we two more scabby sheep, two more social lepers and professional outcasts. If, on the other hand, they are unqualified men (and the man who estimates his own services as low as sixpence is scarcely likely to pay first-class salaries), by what right are they Doctors?

I can see in every week's medical journals complaints of unprofessional behaviour on the part of "gentlemen," but the profession at large has the power to stamp out such practices as these, which are every year lowering the status of a grand and noble profession, and bring not only the perpetrators themselves, but also those who have every disposition to uphold the dignity of their calling, into scorn and disrepute. There are said to be scabby sleep in every flock, but I cannot think very highly of the licensing bodies if they are powerless to put a stop to such unprofessional practices, or too torpid to notice them. There are plenty of restrictions, but no manner of protection.

Let us rather have the honest old barber-surgeon, or the white-aproned apothecary and the open surgery, than "duly qualified" medical "gentlemen" who do not estimate their services at a higher rate than "Advice and medicine, sixpence each bottle"—I enclose my card, and have the honour to remain, sir, your obedient servant, PASQUIN.

*** We have already, some time ago, expressed our opinion of the handbills to which our correspondent refers. They are simply disgraceful. (*British Medical Journal*, 1880.)