We used a square-wave galvanic current as described by Doran *et al.* (1964) because this form of stimulating current is most readily available in standard apparatus and easiest to measure in terms of duration and strength. Nevertheless, there is no reason why other forms of current, sine wave, triangular wave, or square wave of alternating polarity, should not be used, and one of these may ultimately prove more suitable.

The precise mechanism by which muscle stimulation reduces the incidence of deep vein thrombosis remains an unanswered question. Though simple abolition of venous stasis, by increasing the velocity of venous blood flow, may be important, other possible factors are the increase in arterial inflow—normally depressed during operation (Browse, 1962)—induced by the muscle contractions, and an increase in blood fibrinolytic activity which is known to be stimulated by muscle activity (Fearnley, 1965).

It can be argued that most of the deep vein thromboses detected by the ^{125}I-fibrinogen uptake test are small, symptomless, and of little or no consequence to the patient. Even if this is true it is extremely likely that the more extensive dangerous thrombus develops from one of these small initial thrombi.

The venous thrombosis which most often gives rise to fatal pulmonary embolism develops in the upper femoral or iliac veins (Mavor and Galloway, 1967). No such thrombi have been detected in this trial. The ^{125}I-fibrinogen uptake test is not accurate above the groin, but no patient has shown clinical evidence of either iliac vein occlusion or pulmonary embolism. It is reasonable to suppose that the twofold increase in the velocity of venous blood flow in the upper femoral vein produced by calf muscle stimulation will inhibit thrombus formation at this site if it does so in the more distal veins of the thigh and calf.

Pulmonary embolism is a common postoperative complication and has been held responsible for the death of about 1 in every 900 patients undergoing surgical operation (Pilcher, 1937; Murley, 1950), and deep calf vein thrombosis is often followed by venous incompetence which eventually causes chronic swelling and ulceration of the legs. The importance of adequate prophylaxis requires no further emphasis. Several methods of prophylaxis have been described (Browse, 1970). So far only anticoagulants (Sevitt and Gallagher, 1959), calf stimulation, and the infusion of dextran 70 (Ahlberg *et al.*, 1968; Lambie *et al.*, 1970) have shown encouraging results. Possibly the combination of an intravenous agent and calf muscle stimulation would provide the most effective prophylaxis, without the logistic problems and serious complications that abound when anticoagulants are used.

The high incidence of deep vein thrombosis during surgery and the serious effects of thrombus propagation and fragmentation make effective prophylaxis mandatory. This study has shown the simplicity and effectiveness of calf muscle stimulation, and we believe that this method should be used on all patients undergoing a major surgical operation.

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References

Ahlberg, A., Nylander, G., Robertson, B., Cronberg, S., and Nilsson, I. M. (1968). *Acta Chirurgica Scandanavica*, Suppl. No. 387, p. 83.
Armitage, P. (1960). *Sequential Medical Trials*. Oxford, Blackwell Scientific.
Browse, N. L. (1962). *British Medical Journal*, **1**, 1714.
Browse, N. L. (1970). *British Medical Journal*, **2**, 780.
Doran, F. S. A., Drury, M., and Sivyer, A. (1964). *British Journal of Surgery*, **51**, 486.
Doran, F. S. A., and White, H. M. (1967). *British Journal of Surgery*, **54**, 686.
Doran, F. S. A., White, H. M., and Drury, M. (1970). *British Journal of Surgery*, **57**, 20.
Fearnley, G. R. (1965). *Fibrinolysis*. London, Arnold.
Flanc, C., Kakkar, V. V., and Clarke, M. B. (1968). *British Journal of Surgery*, **55**, 742.
Gibbs, H. M. (1959). *British Journal of Surgery*, **47**, 282.
Kakkar, V. V. (1970). Personal communication.
Kemble, J. V. H. (1970). Personal communication.
Lambie, J. M., Barber, D. C., Dhall, D. P., and Matheson, H. A. (1970). *British Medical Journal*, **2**, 144.
Makin, G. S. (1969). *British Journal of Surgery*, **56**, 373.
Mavor, G. E., and Galloway, J. M. D. (1967). *Lancet*, **1**, 871.
Moloney, G. E., and Fell, R. H. (1968). *British Medical Journal*, **4**, 705.
Murley, R. S. (1950). *Annals of the Royal College of Surgeons of England*, **6**, 283.
Negus, D., Pinto, D. J., LeQuesne, L. P., Brown, N., and Chapman, M. (1968). *British Journal of Surgery*, **55**, 835.
Negus, D., Pinto, D. J., and Brown, N. (1969). *Acta Chirurgica Belgica*, **68**, 507.
Nelson, H. (1944). *Archives of Surgery*, **49**, 1.
Pearson, A. (1954). *British Medical Journal*, **1**, 643.
Pilcher, R. (1937). *British Journal of Surgery*, **25**, 42.
Sevitt, S., and Gallagher, N. (1959). *Lancet*, **2**, 981.
Wilkins, R. W., Mixter, G., Stanton, J. R., and Litter, J. (1952). *New England Journal of Medicine*, **246**, 360.

Vitamin B_{12} Excretion in Patients with Various Skin Diseases

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Summary: The excretion in the urine of ^{58}Co after an oral dose of ^{58}Co vitamin B_{12} given together with intrinsic factor has been found to be reduced in a number of patients with psoriasis, eczema, and other less common dermatoses. There is a correlation between the abnormality and the extent of the rash. A reduced glomerular filtration rate was found in a few of the patients in whom it was measured, and this must have been responsible, at least in part, for the reduced excretion of vitamin B_{12} in these patients, but abnormal vitamin B_{12} excretion also occurred in the absence of impaired renal function. Our evidence is insufficient to show whether malabsorption or increased tissue utilization of vitamin B_{12} was the explanation in other cases. Certainly a number of patients had steatorrhoea, and in these it is most likely that malabsorption was the major factor. In patients without steatorrhoea a lone malabsorption of vitamin B_{12} cannot be excluded. A decreased serum concentration of vitamin B_{12} was found in only one of the patients.

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Introduction

Malabsorption is common in patients with skin disease, and we have become particularly interested in a group of patients who develop steatorrhoea as a result of their rash (Shuster and Marks, 1965). This dermatogenic enteropathy has been found most often in patients with eczema and psoriasis, but it occurs also in patients with other dermatoses. Though malabsorption of fat is the commonest biochemical abnormality we have found in these patients, there is evidence in some of them of malabsorption of D-xylose (Shuster and Marks, 1970), folate (I. Kaimis, R. Summerly, and C. Giles, 1970, personal communication), and iron (Marks and Shuster, 1968), of impaired lactose tolerance (P. R. Salmon and A. E. Read, 1970, personal communication), and occasionally of a protein-losing enteropathy (Shuster, 1967). Some preliminary studies of vitamin B_{12} absorption have already been done (Shuster and Marks, 1970) and the present paper describes an extension of these studies.

Patients and Methods

Patients with eczema, psoriasis, lichen planus, pityriasis rubra pilaris, acquired ichthyosis, and Darier's disease admitted to hospital for treatment were studied consecutively so long as they were willing to take part in the investigation. There were 42 patients in all—19 with psoriasis, 16 with eczema, 2 with pityriasis rubra pilaris, 2 with lichen planus, 2 with Darier's disease, and 1 with acquired ichthyosis. Patients were not selected on the basis of symptoms or signs referable to their small intestine, though the fact that they had been admitted to hospital usually meant that their rash was severe or extensive. None of the patients was being treated with methotrexate at the time of the investigation.

In view of the fact that the steatorrhoea of dermatogenic enteropathy is related to the extent of the rash (Marks and Shuster, 1970a) a clinical assessment of the degree of skin surface involved by the rash was made in all cases, and patients were put into one of three groups, according to their clinical state at the time: (1) those with erythroderma or generalized exfoliative dermatitis—100% skin surface involved; (2) those with very limited rashes, usually confined to the hands and feet—less than 10% skin surface involved; and (3) those intermediate between 1 and 2 who had moderately extensive rashes—50 to 75% skin surface involved.

A Schilling test was done in all 42 patients, and in all in whom it was possible the faecal fat excretion was measured and a jejunal biopsy was done. In a number the serum vitamin B_{12} concentration and the endogenous creatinine clearance were also measured.

Schilling Test.—The patient fasted overnight, and in the morning he was given an oral dose of 1 μg. ^{58}Co vitamin B_{12} (Sp.A. 1Ci/g.; Radiochemical Centre, Amersham). A dose of 50 mg. intrinsic factor was given at the same time to exclude decreased absorption from pernicious anaemia. The patient was allowed to eat breakfast an hour later, and one hour after that was given a "flushing dose" of 1,000 μg. vitamin B_{12} by intramuscular injection. A 24-hour collection of urine was made, starting from the time the ^{58}Co vitamin B_{12} was given. In order to reduce to a minimum the human error which may arise in the collection of 24-hour urine samples we have a standard procedure, and this was followed in the present series of patients. We make a point of telling each patient to empty his bladder immediately before the start of the test and again at the end of the 24-hour period, and every effort is made to ensure that there is no loss of urine voided in the intervening time. If in spite of these precautions the urinary volume is less than 1,000 ml. or its creatinine content is less than 1 g. the test is abandoned and repeated on another occasion. Radioactivity due to ^{58}Co was counted in the whole volume of urine with a "ring counter" of eight Geiger-Muller tubes. Normal people excrete 10% or more of the oral dose in 24 hours (Stewart, Pollock, Hoffbrand, Mollin, and Booth, 1967).

Faecal Fat Excretion.—This was measured by the method of Van de Kamer, ten Bokkel Huinink, and Weyers (1949). The patient was on an ordinary ward diet calculated to provide 100 g. of fat/day. Stool collections were made over five days and the mean daily fat excretion was calculated. Normal people excrete 5 g. of fat or less per day in these circumstances.

Serum Vitamin B_{12} Concentration.—This was measured with *Lactobacillus leichmannii* as the test organism. The normal range is 100—1,000 pg./ml.

Endogenous Creatinine Clearance.—Plasma and urinary creatinine were measured by the alkaline picrate method (Varley, 1967). The clearance was calculated over a 24-hour period. The normal range is 100—150 ml./min.

Peroral Biopsy of Upper Small-intestinal Mucosa.—This was done with a Crosby capsule (Crosby and Kugler, 1957). The specimen was taken between the second part of the duodenum and the first few centimetres of the jejunum after the position of the capsule had been checked by an *x*-ray film. The material was processed and examined as described previously and the appearances were classified according to the predominant surface feature (Marks and Shuster, 1970b): convolutions, joined leaves, broad leaves, narrow leaves, and fingers. We regard fingers and all forms of leaves as normal, and convolutions occur as the predominant feature in 8% of our local control population (Marks and Shuster, 1970b).

Results

The percentage of ^{58}Co excreted in the urine in the first 24 hours after the oral dose of ^{58}Co vitamin B_{12} is shown in Fig. 1. Seventeen patients (10 with psoriasis, 6 with eczema, and 1 with pityriasis rubra pilaris) excreted an abnormally low amount of the isotope. There was no significant association ($P>0.1$, calculated by exact table method) between a decreased urinary ^{58}Co excretion and the presence of steatorrhoea, though five of the six patients with steatorrhoea from dermatogenic enteropathy had an abnormal Schilling test; in the other 10 patients with an abnormal Schilling test in whom the faecal fat excretion was measured it was normal (Fig. 2).

Only two patients had a predominantly convoluted mucosa in the upper part of the small intestine, and in both of these the Schilling test was normal (Fig. 3).

There was some correlation between the extent of the rash

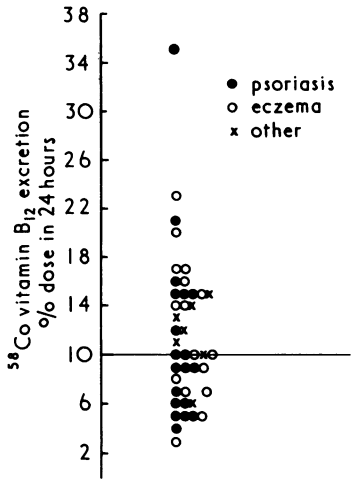

FIG. 1.—Urinary excretion of ^{58}Co vitamin B_{12} in 42 patients with psoriasis, eczema, and other dermatoses.

and vitamin B_{12} excretion: 11 of the 19 patients with 100% skin surface involvement, 4 of the 19 with 50-75% skin surface involvement, and one of the four with less than 10% skin surface involvement excreted an abnormally low amount of ^{58}Co in their urine (Fig. 4). There is a significant difference between the results in those with 100% skin surface involved and those with less extensive skin disease ($t=3{\cdot}3$, $P<0{\cdot}01$). No correlation between the length of history of the dermatosis and the vitamin B_{12} excretion was obvious (Fig. 5), but

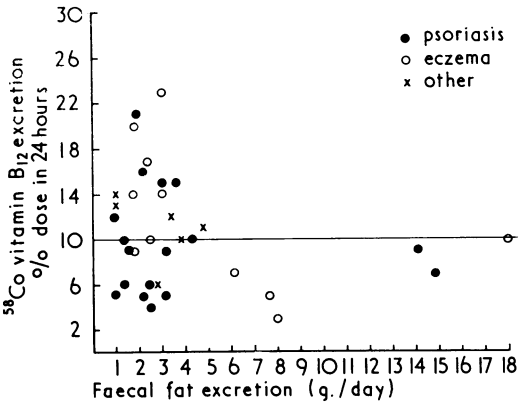

FIG. 2.—Urinary excretion of ^{58}Co vitamin B_{12} and faecal excretion of fat in 34 of the patients shown in Fig. 1.

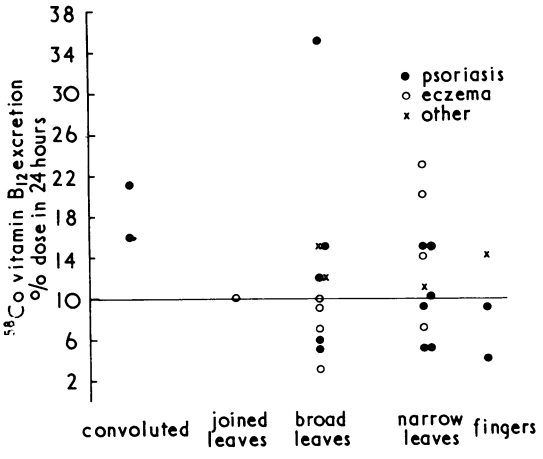

FIG. 3.—Urinary excretion of ^{58}Co vitamin B^{12} and predominant stereomicroscopic appearance of jejunal mucosa in 28 of the patients shown in Fig. 1.

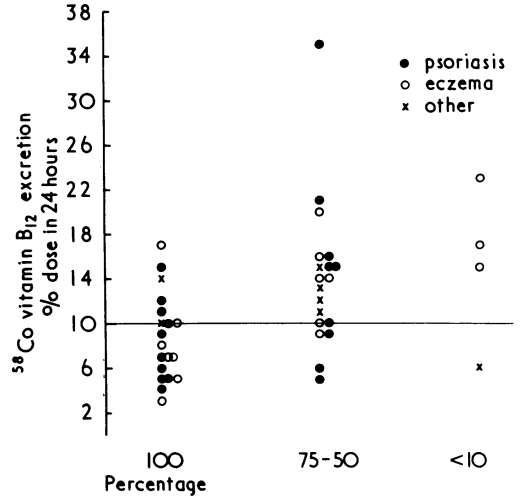

FIG. 4.—Urinary excretion of ^{58}Co vitamin B^{12} and extent of rash in patients shown in Fig. 1.

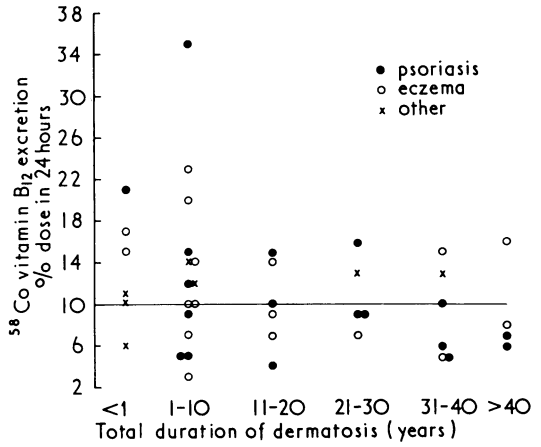

FIG. 5.—Urinary excretion of ^{58}Co vitamin B^{12} and total duration of dermatosis in patients shown in Fig. 1.

we cannot exclude the possibility that duration of disease had an effect which was obscured by other variables such as the extent of the rash. Other factors which may be relevant to the excretion of ^{58}Co vitamin B_{12} after an oral dose include the age of the patient and his glomerular filtration rate (see below). The information available on these points is included in the Table, which gives details of the 17 patients with a decreased urinary ^{58}Co excretion and shows that the abnormality of vitamin B_{12} excretion was not confined to the elderly and occurred in the presence of a normal glomerular filtration rate.

The serum vitamin B_{12} concentration was normal in all but one of the patients examined (Fig. 6). This patient (Case 5 in the Table) had had eczema for 40 years in all and was erythrodermic at the time of his study. He also had steatorrhoea as a result of dermatogenic enteropathy.

Discussion

Urinary excretion of ^{58}Co vitamin B_{12} after an oral dose of the substance given together with intrinsic factor has been found to be impaired in a number of patients with various dermatoses, especially those in whom the rash is extensive. Though the test is commonly used as a measure of vitamin B_{12} absorption from the small intestine, renal excretion of the vitamin will also influence the result. Vitamin B_{12} is cleared by glomerular filtration, and its excretion is decreased in patients with glomerular disease (Rath, McCurdy, and Duffy, 1957). Glomerular filtration rate is usually normal in patients with skin disease though in erythroderma renal blood flow may be diminished (Shuster and Marks, 1970). Renal function,

Details of 17 Patients with Decreased Urinary ^{58}Co Excretion

Case No.	Sex and Age	Diagnosis	% Skin Surface Involved by Rash	Faecal Fat Excretion (g./day)	Endogenous Creatinine Clearance (ml./min.)	^{58}Co Vitamin B^{12} Excretion (% Dose in 24 Hours)
1	M. 67	Eczema	100	8·0	147	3
2*	M. 73	Psoriasis	100	2·5	10	4
3	F. 51	Psoriasis	100	2·2	—	5
4	F. 26	Psoriasis	100	1·0	—	5
5	M. 68	Eczema	100	7·7	80	5
6	M. 66	Psoriasis	100	1·4	—	6
7	M. 75	Eczema	100	14·9	—	7
8*	F. 69	Psoriasis	100	—	38	7
9	M. 59	Eczema	100	6·2	125	7
10	F. 54	Eczema	100	—	—	8
11	M. 62	Psoriasis	100	14·1	—	9
12	M. 52	Psoriasis	100	3·2	155	9
13	M. 47	Psoriasis	75—50	3·1	125	5
14	M. 60	Psoriasis	75—50	2·5	65	6
15	M. 49	Eczema	75—50	1·8	—	9
16	M. 56	Psoriasis	75—50	1·6	—	9
17	F. 35	Pityriasis rubra pilaris	<10	2·9	—	6

*These two patients were in heart failure from their erythroderma at the time of the test.

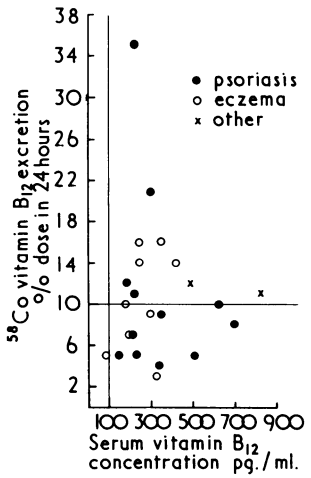

FIG. 6.—Urinary excretion of ^{58}Co vitamin B_{12} and serum vitamin B_{12} concentration in 23 of the patients shown in Fig. 1.

including glomerular filtration, deteriorates with age, and a number of our patients were elderly. Nevertheless, reduced glomerular filtration is not the only explanation of the abnormal Schilling tests in our patients, as we found the abnormality in some patients with a normal endogenous creatine clearance.

Before we can accept that our results indicate an abnormality of vitamin B_{12} absorption a further factor has to be considered, and this is altered vitamin B_{12} metabolism. It has been found that the concentration of vitamin B_{12} in the skin is reduced in patients with psoriasis (Stankler, 1969) and this could indicate increased metabolism, presumably as a result of the increased skin cell turnover in this condition (Porter and Shuster, 1968) and perhaps analogous to the altered folate metabolism present in certain skin diseases (Knowles, Shuster, and Wells, 1963; Shuster, Marks, and Chanarin, 1967). The dose of inert vitamin B_{12} given two hours after the ^{58}Co vitamin B_{12} normally releases any ^{58}Co vitamin B_{12} taken up into the body stores. We do not know whether in our patients ^{58}Co vitamin B_{12} is taken up by the diseased skin and perhaps utilized there preferentially and therefore no longer available for release two hours later when the "flushing" dose of vitamin B_{12} is given. If this were so, such a metabolic abnormality could explain the decreased excretion.

There is nothing in our findings which is inconsistent with the possibility that they are due to malabsorption from dermatogenic enteropathy, and the fact that so many of the patients with steatorrhoea had an abnormal Schilling test suggests that this may well be important. The normal jejunal biopsy findings are consistent with this diagnosis (Marks and Shuster, 1970a), and the absence of steatorrhoea in most patients with an abnormal Schilling test does not exclude the possibility of vitamin B_{12} malabsorption in them, especially in view of the different sites of absorption of fat and vitamin B_{12}. The relationship of the abnormal vitamin B_{12} excretion to the extent of the rash does not help in the localization of the abnormality to the gut or the skin, as many of the systemic effects of skin disease are so related (Shuster, 1967; Shuster and Marks, 1970). From the present study it is impossible to say what the mechanism of the abnormality is, and further studies, including plasma disappearance of vitamin B_{12} and direct examination of the bowel, are being undertaken. It is possible that malabsorption, increased metabolism, and impaired renal excretion all contribute in some patients.

A decreased vitamin B_{12} concentration in the serum and the accompanying effects on the bone marrow and central nervous system do not as a rule appear to be a problem in patients with eczema and psoriasis. Anaemia with megaloblastic erythropoiesis may occur, but all cases up to now have been explicable on the basis of folic acid deficiency (Shuster *et al.*, 1967). Nevertheless, it is possible that vitamin B_{12} deficiency with its consequences may arise, especially in patients with extensive rashes of long duration.

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References

Crosby, W. H., and Kugler, H. W. (1957). *American Journal of Digestive Diseases*, **2**, 236.
Knowles, J. P., Shuster, S., and Wells, G. C. (1963). *Lancet*, **1**, 1138.
Marks, J., and Shuster, S. (1968). *Archives of Dermatology*, **98**, 469.
Marks, J., and Shuster, S. (1970a). *Gut*, **11**, 281.
Marks, J., and Shuster, S. (1970b). *Gut*, **11**, 292.
Porter, D., and Shuster, S. (1968). *Archives of Dermatology*, **98**, 339.
Rath, C. E., McCurdy, P. R., and Duffy, B. J. (1957). *New England Journal of Medicine*, **256**, 111.
Shuster, S. (1967). *Lancet*, **1**, 907.
Shuster, S., and Marks, J. (1965). *Lancet*, **1**, 1367.
Shuster, S., and Marks, J. (1970). *Systemic Effects of Skin Disease*. London, Heinemann Medical.
Shuster, S., Marks, J., and Chanarin, I. (1967). *British Journal of Dermatology*, **79**, 398.
Stankler, L. (1969). *British Journal of Dermatology*, **81**, 911.
Stewart, J. S., Pollock, D. J., Hoffbrand, A. V., Mollin, D. L., and Booth, C. C. (1967). *Quarterly Journal of Medicine*, **36**, 425.
Van de Kamer, J. H., ten Bokkel Huinink, H., and Weyers, H. A. (1949). *Journal of Biological Chemistry*, **177**, 347.
Varley, H. (1967). *Practical Clinical Biochemistry*, 4th ed., p. 197. London, Heinemann.