The United States Public Health Service (1957) reckon that isoniazid is 80% effective in preventing serious extrapulmonary complications. The follow-up is short, being at the most 30 months.

In the second outbreak mentioned, the bovine strain of tubercle bacilli was found in the slaughtered cows and, as no human source of infection could be found after an intensive search, it is reasonable to conclude that almost certainly the herd infection was due to a bovine source. One must also infer that the high percentage of tuberculin-positive reactors who had been consuming the herd milk, were also infected with the bovine strain of tubercle bacilli.

The dangers of recent and late disseminated tuberculous foci as described led to the decision that chemoprophylaxis should be given. From a long-term point of view nothing is known of the value of such prophylaxis, but the administration of isoniazid seems very worth while as it is an effective anti-tuberculous agent and as it diffuses into all tissues and fluids and into dense caseous lesions in high concentration (Barclay *et al.*, 1953).

To reduce the risk of resistant tubercle bacilli the isoniazid was combined with P.A.S. It would appear that children do not tolerate P.A.S. much better than adults and that preparations of the pycamisan type are not very suitable for mass prophylaxis.

Conclusion

The finding of a high percentage of positive tuberculin reactors among persons who had recently ingested untreated milk derived from tuberculin-positive cattle led to the decision that treatment should be offered to reduce the risk of subsequent disseminated tuberculosis.

The chemotherapy had untoward effects in an unexpectedly large number of children and so the dangers of inadequate treatment and dosage are very real. We believe that prophylactic treatment requires as careful supervision as routine therapy.

Close liaison between the Ministry of Agriculture, the medical officer of health, and the chest physician is of paramount importance. It is essential that the medical officer of health should be informed at once of any possible tuberculous infection which might directly or indirectly endanger the milk supply, so that appropriate public health measures may be instituted.

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THERAPEUTIC EFFECT, UTILIZATION, AND FATE OF INJECTED VITAMIN B₁₂ IN MAN

A PRELIMINARY REPORT

BY

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During studies on the utilization of injected vitamin B₁₂ in man, it was observed that an injection of 1,000 µg. of vitamin B₁₂ given intramuscularly did not maintain the serum vitamin B₁₂ level above the pre-injection level, or above the lower limit of normal, for much longer than an injection of 50 or 100 µg. given intramuscularly. It seemed likely that this might be due simply to the increased amount excreted after the larger injection. Detailed investigations, however, have shown that this is not the case and that the duration of effect of a large dose of vitamin B₁₂ is much less than might be expected from the duration of effect of a small dose, even when allowance is made for the amounts excreted after injection.

Observations made on six patients which demonstrate this phenomenon clearly form the basis of this paper.

Patients, Materials, and Methods

The diagnosis of Addisonian pernicious anaemia was established in all patients on the basis of a macrocytic anaemia, megaloblastic bone-marrow, histamine-fast achlorhydria, low serum vitamin B₁₂ level, and response to parenteral vitamin B₁₂ only when they first came under observation. Absorption studies with radioactive vitamin B₁₂ alone and with intrinsic factor were performed in all cases and confirmed the diagnosis. The patients were treated with parenteral vitamin B₁₂ for several months, and then treatment was withheld and the serum vitamin B₁₂ level estimated regularly. When the level fell to an arbitrary figure, usually about 140 µg./ml., which is the lower limit of normal by the method used, the patient was given an injection of Co-58 vitamin B₁₂, 1,000 µg. 0.2 µc, or 100 µg. 0.2 µc, or 50 µg. 0.3 µc. The urine excreted in the subsequent 24 hours was collected, the radioactivity in an aliquot counted, and the total radioactivity calculated. This was taken to be a true measure of the amount of vitamin B₁₂ excreted in the urine: the proof of this theory and the methods used are described in detail elsewhere (Adams, 1961).

After the first injection of Co-58 vitamin B₁₂ the serum vitamin B₁₂ level was estimated regularly, and when the level fell to about the original pre-injection level a second injection of Co-58 vitamin B₁₂ was given and the cycle repeated. At the end of the period of observation all samples of serum obtained during the study were assayed in two different assay batches by a modification of the methods of Ross (1952) and of Hutner *et al.* (1956), using *Euglena gracilis* 3 strain as the test organism; the results presented here are based on the mean values of these two assays.

Results

Results in six cases are shown in graphical form in Figs. 1-6, and more detailed results from the same patients are set out in Tables I and II. In the figures the amount of vitamin B₁₂ retained is shown in

parentheses after the amount injected. The utilization of the Co-58 vitamin B₁₂ retained in the body was calculated from the formula:

$$(\text{amount of vitamin B}_{12} \text{ injected} - \text{amount of Co-58 vitamin B}_{12} \text{ excreted}) \div \text{duration of effect in days.}$$

TABLE I

Case No.	Pre-injection Serum Vitamin B ₁₂ Level (μg./ml.)	Co-58 Vitamin B ₁₂		Time in Days for Serum Vitamin B ₁₂ Level to Fall to 140 μg./ml.	
		Injected (μg.)	Retained (μg.)	140 μg./ml.	Pre-injection Level
1	(1) 127	50	36	35+	35+
	(2) 153	1,000	337	70	58
2	(1) 126	100	57	26	33
	(2) 123	1,000	330	46	60
3	(1) 147	100	51	40	39
	(2) 134	1,000	290	56+	56+
4	(1) 125	1,000	320	38	53
	(2) 109	100	58	35	49+
5	(1) 129	1,000	161	51	53
	(2) 113	100	53.7	42	35+
6	(1) 212	1,000	310	—	52
	(2) 199	100	60	—	40

TABLE II.—Utilization of Co-58 Vitamin B₁₂ Retained

Case No.	After 50 or 100 μg. Injection		After 1,000 μg. Injection	
	(a) Taking 140 μg./ml. Serum Vitamin B ₁₂ as Base-line (μg./Day)	(b) Taking Pre-injection Serum Vitamin B ₁₂ as Base-line (μg./Day)	(a) Taking 140 μg./ml. Serum Vitamin B ₁₂ as Base-line (μg./Day)	(b) Taking Pre-injection Serum Vitamin B ₁₂ as Base-line (μg./Day)
1	<1.0	<1.0	4.8	5.8
2	2.0	1.7	7.1	5.5
3	1.2	1.2	5.0	5.0
4	1.6	1.1	8.6	6.0
5	1.2	1.5	3.0	3.0
6	—	1.5	—	5.9

Discussion

In every case the duration of effect of the 1,000 μg. injection in maintaining the serum vitamin B₁₂ level above the pretreatment level, or above the lower limit of normal (140 μg./ml.), was never greater than twice the effect obtained from 100 μg. or 50 μg. injection in spite of the fact that the amount of vitamin B₁₂ retained in the body after the large injection was three to ten times greater than the amount retained after the small injection (Figs. 1-6; Table I). In other words, the effect of an injection of vitamin B₁₂ in maintaining serum vitamin B₁₂ levels above the pretreatment level or above the lower limit of normal is not proportional to the amount of vitamin B₁₂ retained in the body after an injection.

There seems to be no doubt about the findings. So far as is possible the injections were given at the same serum vitamin B₁₂ level in each patient, and the same pattern was seen whether the small injection was given before or after the large injection. The possibility that urinary excretion of the injected Co-58 vitamin B₁₂ continued for more than 24 hours after injection was investigated in detail and was not found to be a significant factor. The intestinal excretion of injected Co-58 vitamin B₁₂ in the doses used is trivial (unpublished observations) and can be disregarded as a relevant factor. It is known that Co-58 vitamin B₁₂ may undergo deterioration *in vitro* (Lester Smith, 1959), and the possibility that this was a factor was also considered: the repetition of the pattern in every case studied was taken as evidence against this, and additional evidence was obtained when it was found that in two cases a

FIG. 1.—Case 1.

FIG. 2.—Case 2.

FIG. 3.—Case 3.

FIG. 4.—Case 4.

FIG. 5.—Case 5.

FIG. 6.—Case 6.

sample of the Co-58 vitamin B₁₂ injected had not lost any of its microbiological activity between the time of use and the time the samples of sera were assayed.

The significance of the findings cannot be established with certainty in the light of our present knowledge of the metabolism of vitamin B₁₂. It has already been suggested that vitamin B₁₂ does not exist as such in man but as an active derivative (Adams, 1961). The findings reported here raise the possibility that, at least with injection of large amounts of vitamin B₁₂, there may be a second metabolic pathway which involves conversion of the injected vitamin to an inactive form.

For practical purposes these patients with Addisonian pernicious anaemia do not absorb vitamin B₁₂ from the intestine, and their intake of vitamin B₁₂ is by injection; one might expect, therefore, that the utilization of injected vitamin B₁₂ obtained from the formula used might represent the physiological requirement for vitamin B₁₂ in man. It is scarcely likely that the physiological requirement varies with the amount of vitamin B₁₂ injected, and one must conclude that the physiological requirement for vitamin B₁₂ and the utilization of injected vitamin B₁₂ as defined here are not necessarily the same, although this may be the case at certain lower dosage levels.

The aim of treatment of a patient with Addisonian pernicious anaemia is to achieve and maintain a serum vitamin B₁₂ level within the normal range. It is obvious from the results that relatively little is to be gained by using an injection of 1,000 µg. in preference to an injection of 100 µg. The results reported here, and those obtained from a larger series of patients still under observation, tend to confirm the view that an injection of 100 µg. of vitamin B₁₂ every three to five weeks is an economical and adequate maintenance treatment in most patients with pernicious anaemia.

Summary

A study of six patients with Addisonian pernicious anaemia has shown that large injections (1,000 µg.) of vitamin B₁₂ do not have the expected effect in maintaining serum vitamin B₁₂ levels above the lower limit of normal as compared with the effect of small (50 or 100 µg.) injections of vitamin B₁₂. This phenomenon is not due to the larger amount excreted after the 1,000 µg. injection, and it is possible that in the case of the larger injection at least some of the injected vitamin B₁₂ may be inactivated in the body. From the results it appears that 100 µg. intramuscularly every three to five weeks is the most economical and effective form of maintenance therapy in patients with pernicious anaemia.

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The Nuffield Provincial Hospitals Trust has made a grant of £3,500 over the next three years to enable the Bristol Industrial Therapy Organization to start a workshop for psychiatric patients who are well enough to leave hospital but not able to compete in open employment.

E

Preliminary Communications

Simultaneous Intramuscular Injection of Oxytocin and Ergometrine : A Tocographic Study

Responsible obstetric opinion in regard to the management of the third stage of labour and the treatment of post-partum haemorrhage has undergone some modification in recent years. Ergometrine, for long the sheet anchor of treatment in post-partum haemorrhage, is no longer condemned before delivery of the placenta, but is injected at the first sign of bleeding. Moreover, in many hospitals throughout this country nowadays, ergometrine is given routinely, intramuscularly or intravenously, as soon as the head is delivered. Those who practise the method emphatically believe that its use brings a rewarding reduction in the incidence of post-partum haemorrhage and in the size of the haemorrhage when it occurs—and that imprisonment of the placenta occasionally is a small price to pay for this reward.

Oxytocin—which might be regarded as more physiological—has not been generally favoured in this connexion, chiefly because, in the past, profound shock has occasionally followed its use. But there is little doubt that many of the mishaps of former years occurred with the old "puitrin," and some were the result of misuse of the drug, sometimes amounting to irresponsibility, with too large and often-repeated dosage. Moreover, it must be remembered that the pure preparations of oxytocin now available are probably safer than those formerly used. In the United States of America oxytocin is employed a good deal in the conduct of the third stage of labour.

Case No.	Day of Puerperium	Details of Injection and Dose	Time of Onset of Oxytocic Response
Main Series			
1	7	Oxytocin 2.5 u. Ergometrine 0.25 mg.	3' 40"
2	6	" "	3' 30"
3	3	" "	2' 30"
4	6	" "	2' 0"
5	6	" "	1' 50"
6	2	" "	1' 20"
7	3	" "	1' 30"
8	2	" "	2' 30"
9	2	" "	3' 10"
10	2	" "	2' 40"
11	3	" "	3' 0"
12	2	" "	3' 40"
13	3	Oxytocin 5 u. Ergometrine 0.5 mg.	3' 30"
14	3	" "	2' 10"
15	7	" "	2' 0"
16	3	" "	2' 20"
17	9	" "	4' 30"
18	7	" "	1' 20"
Control Series			
19	3	Oxytocin 5 u.	2' 40"
20	3	" "	4' 0"
21	2	" "	3' 10"
22	3	" "	2' 20"
23	2	" "	2' 0"
24	2	" "	3' 0"
25	3	" "	2' 10"
26	3	" "	4' 0"
27	3	" "	1' 30"
28	2	" "	1' 10"
29	6	Oxytocin 2.5 u.	2' 30"
30	3	" "	2' 0"

Mean of main series = 2 min. 37 sec. (S.D. 55 sec.)
 " " control " = 2 " 32 " (" 53 ")