

Vitamin B₁₂ absorption in tobacco amblyopia

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It is well established that a proportion of patients with tobacco amblyopia have pernicious anaemia or some other demonstrable defect of vitamin B₁₂ metabolism (Leishman, 1951; Heaton, McCormick, and Freeman, 1958; Freeman and Heaton, 1961; Foulds, Chisholm, Brontë-Stewart, and Wilson, 1968). We have examined 65 cases of tobacco amblyopia diagnosed according to the criteria of Heaton and others (1958) for evidence of defective vitamin B₁₂ metabolism, with particular reference to vitamin B₁₂ absorption.

Material

All the 65 patients studied had classical tobacco amblyopia with characteristic field defects, reduced central vision, and an acquired defect of red/green colour discrimination. All but one were males, the ages ranging from 49 to 84 years (mean 66 ± 9.3), and the majority were pipe smokers (two male patients smoked cigarettes exclusively as did the one female patient in the series, one patient smoked cigars only, and five patients smoked both cigarettes and a pipe).

Estimations of serum B₁₂ were carried out by the *Euglena gracilis* assay of Ross (1952) and Schilling tests of B₁₂ absorption as described by Schilling (1953). The dietary intake of B₁₂ with estimated loss in cooking was assessed by the hospital dietician. Intestinal absorption was measured by the xylose absorption test (Helmer and Fouts, 1937).

Other investigations included full haematological examination of all patients and examination of the sternal marrow in those with anaemia (Hb < 10 g. per cent.) or with a level of B₁₂ in the serum of < 150 $\mu\mu\text{g./ml.}$ Where the Schilling test showed less than 12 per cent. recovery of Co⁵⁸-labelled B₁₂, it was repeated with added intrinsic factor.

Results

SERUM VITAMIN B₁₂ LEVEL

This was determined in 62 of the 65 patients; it was below 100 $\mu\mu\text{g./ml.}$ in nine and below 150 $\mu\mu\text{g./ml.}$ in 23 of them. It was assumed to be below 150 $\mu\mu\text{g./ml.}$ in a further three patients in whom a clinical diagnosis of pernicious anaemia was made without a determination of serum B₁₂ level. Taking values of 150 $\mu\mu\text{g./ml.}$ and below as abnormal, 26 of the 65 amblyopes (40 per cent.) had reduced levels. The values recorded ranged from 30 to 520 $\mu\mu\text{g./ml.}$ (mean 196 ± 119). This is significantly lower* than the mean value of 237 $\mu\mu\text{g./ml.} \pm 119$ found in a group of 72 non-amblyopic subjects, thus confirming the findings of Heaton and others (1958). The subjects in this control group were drawn from those over 45 years of age attending the Tennent Institute of Ophthalmology with conditions other than tobacco amblyopia. In age composition the groups matched,** but the control group included smokers and non-smokers.

DIETARY INTAKE

It was found impossible to estimate accurately the true dietary intake of vitamin B₁₂, but evidence suggesting a poor intake was obtained in 25 per cent. of the amblyopes examined.

VITAMIN B₁₂ ABSORPTION

Schilling tests were performed on 46 of the 65 amblyopes. Values of < 12 per cent. recovery were found in 21 (45.7 per cent.) and of less than 5 per cent. in six (13 per cent.). Xylose absorption tests were carried out on 33 amblyopic patients and an abnormal result (*i.e.* < 3 g. per cent. in the urine) was found in six patients (18 per cent.) while border-line figures (3 to 4 g. per cent. in the urine) were found in a further three (9 per cent.).

VITAMIN B₁₂ IN RELATION TO TOBACCO CONSUMPTION

In an attempt to determine whether the low level of serum B₁₂ found in 40 per cent. of the tobacco amblyopes was the result of tobacco smoking or an independently determined factor, the tobacco consumption in these patients was plotted against the serum B₁₂ level (Fig. 1), when it could be seen that there was a significant though not very close positive correlation between these factors ($r = +0.384$; $n = 53$, $P = < 0.01$). In this group of patients tobacco amblyopia occurred with a low consumption of tobacco, where the serum B₁₂ level was low, a much higher consumption of tobacco being the rule when the serum B₁₂ level was in the normal range. A similar trend was noted in the case of tobacco consumption and the results of the Schilling test in these patients (Fig. 2) where poor absorption of B₁₂ tended to be associated with low levels of tobacco consumption and vice versa. The correlation is less close than for serum B₁₂ ($r = +0.330$), but is significant ($n = 40$; $P = < 0.05$).

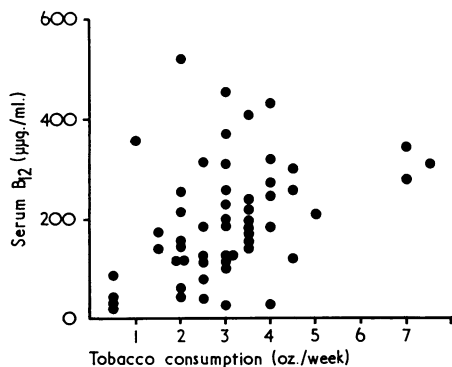


FIG. 1 Serum vitamin B₁₂ and tobacco consumption in tobacco amblyopia

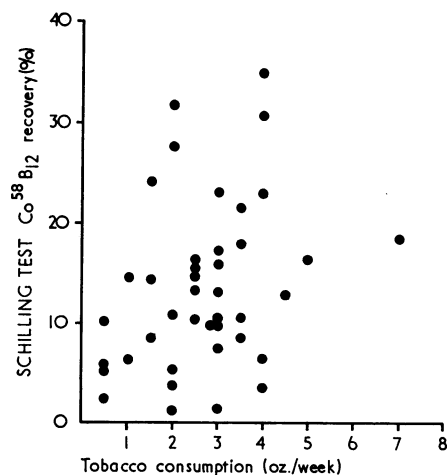


FIG. 2 Vitamin B₁₂ absorption and tobacco consumption in tobacco amblyopia

Surprisingly, a similar trend was noted when the results of the xylose absorption tests in tobacco amblyopes were compared with tobacco consumption (Fig. 3, opposite). The correlation coefficient in this instance however, was only $+0.234$, which fails to be significant ($P = > 0.10$).

To test whether the relationship between tobacco consumption and serum B₁₂ level was common to all smokers or only amblyopes, a comparison was made between the tobacco consumption and serum B₁₂ level of 28 male non-amblyopic pipe smokers of similar age to the amblyopic patients (mean 64.9 years, range 43–82) (Fig. 4). No significant correlation either positive or negative was found ($r = -0.001$).

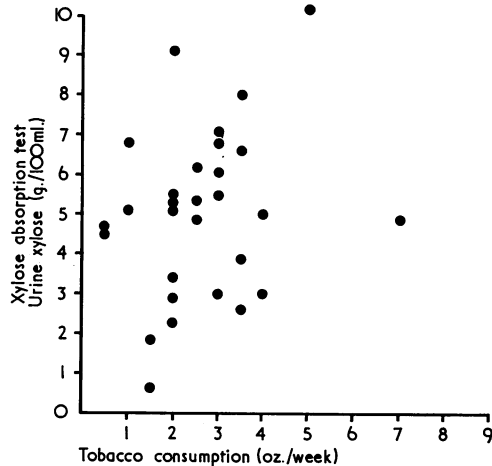


FIG. 3 Intestinal absorption and tobacco consumption in tobacco amblyopia

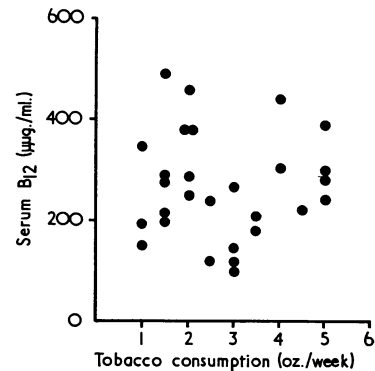


FIG. 4 Serum vitamin B₁₂ and tobacco consumption in normal pipe-smokers

One additional comparison was made. The mean serum B₁₂ level in a group of non-smoking patients was compared with that of pipe-smoking non-amblyopic subjects. Both groups were drawn from a hospital population and consisted of patients in the same age range as the tobacco amblyopes who were attending hospital with eye conditions other than tobacco amblyopia. In the non-smoking group there were 43 subjects and in the pipe smoking group 28 subjects. The mean serum B₁₂ level in the former group was 228 $\mu\text{g./ml.} \pm 116$, and in the latter 269.5 $\mu\text{g./ml.} \pm 101$. There is no significant difference in the mean serum B₁₂ levels of the two groups (" t " = 1.55; $n = 67$; $P = > 0.1$). The mean serum B₁₂ level in the pipe-smoking control group is however significantly greater than in the group of patients with tobacco amblyopia (" t " = 2.79; $n = 81$; $P = < 0.01$). The consumption of tobacco in the group of non-amblyopic pipe smokers was not significantly different from that of the amblyopic group of patients (mean tobacco consumption of the control group 2.73 oz. per week ± 1.32 and of the amblyopic group 3.04 oz. per week ± 1.44 ; " t " = 0.30; $n = 81$; $P = > 0.1$).

Discussion

From our results tobacco amblyopia is a condition which most readily develops in patients whose dietary B₁₂ or B₁₂ absorption is for some reason defective and in such patients amblyopia may develop even when the consumption of tobacco is only moderate (< 10 cigarettes per day in one of our patients). Patients with normal B₁₂ absorption and normal levels of B₁₂ in the serum may also develop amblyopia if they smoke heavily enough. These facts would fit the suggestion that tobacco amblyopia is the result of a failure to detoxify cyanide derived from tobacco smoke (Wokes, 1958; Smith, 1961) and that B₁₂, particularly in its hydroxy form, is necessary for this detoxification (Smith, 1968).

If this is true then it is not surprising that smoking patients with low serum B_{12} levels due to dietary lack or malabsorption of B_{12} should develop this disease, or that there should be a direct relationship between the amount of tobacco required to induce this condition and the amount of available B_{12} . That patients with normal serum B_{12} levels should also develop amblyopia if their tobacco consumption is high enough, might be explained as suggested by Smith (1961) that in such patients much of the available B_{12} has been converted to cyanocobalamin and is therefore unable to detoxify further cyanide, or that as cyanocobalamin it is unable to support certain aspects of optic nerve metabolism.

It is known that patients with tobacco amblyopia, whether overtly B_{12} deficient or not, recover vision on treatment with hydroxocobalamin (and not cyanocobalamin) even if smoking is continued (Chisholm, Brontë-Stewart, and Foulds, 1967), and from this alone it is evident that in these patients, although there may be no apparent B_{12} deficiency, there must be a relative deficiency of B_{12} , or of some B_{12} fraction.

The development of tobacco amblyopia, however, cannot be merely the consequence of a high cyanide intake in the presence of B_{12} depletion for the correlation between tobacco intake and serum B_{12} levels is not very close. In addition we have examined several patients with pernicious anaemia who are also heavy smokers and who have shown no discoverable disturbance of visual function. If B_{12} deficiency and heavy tobacco consumption were the sole factors in the production of amblyopia, such patients would inevitably develop the condition.

It has been suggested that tobacco consumption itself may depress B_{12} absorption, Leishman (1951) suggesting that swallowed products of pipe smoking might inhibit gastric secretion while more recently Phillips and Ainley (1968) have claimed that tobacco smoking depresses B_{12} absorption as shown by the Schilling test. Our results do not support these views. We have found no difference in the serum B_{12} levels of smoking and non-smoking subjects and no correlation could be demonstrated between tobacco intake and serum B_{12} level in healthy pipe smokers. In amblyopic patients on the contrary, both B_{12} absorption and serum levels varied directly with tobacco consumption, the reverse of what would be expected had tobacco intake been a significant factor in depressing B_{12} absorption. From our results it would appear that a depressed absorption of B_{12} as shown by the Schilling test or by low levels of B_{12} in the serum, is an independently determined factor which is nevertheless of aetiological significance in relation to the development of amblyopia. The trend towards a correlation between intestinal absorption, as shown by the xylose absorption test, and tobacco consumption in patients with tobacco amblyopia is comparable to the results of the Schilling test, the xylose absorption test in this instance probably giving a measure of intestinal absorption of B_{12} , particularly in those patients whose faulty B_{12} absorption is not due to a specific defect such as Addisonian pernicious anaemia.

Summary

Schilling tests of vitamin B_{12} absorption, xylose tests of intestinal absorption, and measurements of serum vitamin B_{12} were carried out in a group of 65 patients suffering from tobacco amblyopia. Serum vitamin B_{12} estimations were also made on a group of non-amblyopic pipe-smoking patients and in a similar group of non-smoking patients.

40 per cent. of tobacco amblyopes showed reduced serum levels of vitamin B_{12} and 45 per cent. had defective vitamin B_{12} absorption. Serum vitamin B_{12} levels in tobacco amblyopes were significantly lower than in non-amblyopic subjects.

Serum vitamin B₁₂ levels were similar in non-amblyopic smokers and non-smokers.

In tobacco amblyopia a direct relationship was found to exist between tobacco consumption on the one hand and vitamin B₁₂ absorption and serum vitamin B₁₂ level on the other, amblyopia occurring with low tobacco consumption where vitamin B₁₂ absorption was poor or the serum vitamin B₁₂ level low, a high consumption being necessary where the serum vitamin B₁₂ level was high.

The significance of the findings is discussed in relation to the aetiology of tobacco amblyopia.

The estimations of serum B₁₂ were carried out by Dr. J. S. Adams, consultant physician, Southern General Hospital, Glasgow, to whom we owe a debt of gratitude. Our thanks are due to the nursing staff of the Tennent Institute of Ophthalmology for their help with the xylose absorption and Schilling tests, and also to Miss S. Preston, dietician to the Western Infirmary, Glasgow. We are also grateful to Dr. J. Morrow, who carried out some of the haematological investigations. The figures were prepared by the Department of Medical Illustration, University of Glasgow, and we are grateful to Mr. G. Donald for putting the facilities of his department at our disposal. We acknowledge with gratitude the co-operation of many ophthalmic surgeons of the Western Region who kindly referred cases of tobacco amblyopia to us for study.

Financial support for this research was received from the Medical Research Council and from Glaxo, Ltd., to each of whom we record our gratitude.

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