This finding I think is very significant as showing that diet cannot be paramount in the control of this condition but only contributory. My own conception is that there may also be either a direct hormonal influence or possibly some indirect influence through, for example, water balance. There is evidence in young adults who do not normally exhibit changes in myopia that when these changes do occur they are very frequently synchronous with rapid weight increase. I have digressed somewhat from the subject of protein and its association with myopia, but although the connexion eludes me I feel that as protein has a well-known connexion with fluid balance there may well be some interrelationship between increase in myopia, changes in weight and the hormonal control of growth in which the protein intake and associated interrelationships might play a part.

In conclusion, I am most grateful to The Nutrition Society for its farsightedness in promoting a discussion on this subject.

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Vitamin B_{12} and the eye

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The main ocular conditions in which vitamin B_{12} has been suggested to play an important part are diabetic retinopathy and certain cases of optic neuritis.

Diabetic retinopathy

The position as regards vitamin B_{12} and diabetes is in a state of flux at present. That diabetics have an abnormality in vitamin B_{12} metabolism was first postulated by Becker, Lang & Chow (1953). They observed that in diabetics without retinopathy urinary excretion of an injected dose of vitamin B_{12} was subnormal whereas in those with retinopathy excretion was abnormally high. Support for this finding came from Stone & Chow (1957), who studied urinary excretion of radioactive vitamin B_{12} given by mouth using the method of Schilling. Also Chow, Rosen & Lang (1954) reported that patients with retinopathy have a significantly higher serum vitamin B_{12} level than those without it.

Recently Halsted, Carroll & Rubert (1959) found that diabetic patients with retinopathy and proven renal disease have a significantly higher serum-vitamin B_{12} level than those with or without retinal lesions but no renal disease. As renal insufficiency has been shown to reduce urinary excretion of cobalt-labelled vitamin B_{12},

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they suggest that the known association of retinopathy with renal disease could explain the raised serum-vitamin B_{12} level in diabetic retinopathy. However, this theory predicts findings diametrically opposite to those of Becker *et al.* (1953) and Stone & Chow (1957) who, as stated above, found a high rate of excretion of vitamin B_{12} in diabetic retinopathy. Also three papers have appeared in the last few years in which the authors state that they failed to find any relationship between vitamin B_{12} excretion and retinopathy (Bookman, Joelson, Toll, Baker & Dolger, 1957; Field, Federman, McDaniel & Bakerman, 1957; Boger, Heinrich & Sauer, 1958).

Perhaps one reason why such divergent results have been obtained is that it has only recently been found that vitamin B_{12} labelled with any of the radioactive cobalt isotopes is liable to decompose on storage (E. L. Smith, 1959); hence stocks should be retested for radiochemical purity at intervals of 1 month or less. There is no evidence that workers on vitamin B_{12} and diabetes took these precautions.

When these alterations in vitamin B_{12} metabolism were first discovered it was hoped that vitamin B_{12} therapy might improve diabetic retinopathy in some way; however, only one controlled trial has been done. Keen & Smith (1959) found that 150 μg vitamin B_{12} daily, given by mouth to twelve patients for a year, gave them no advantage over thirteen controls.

Optic neuritis

Mackenzie (1854) was one of the first writers to note the importance of nutrition in some cases of optic neuritis. Since then a search has been made for the specific nutritional factors concerned and in the last 30 years interest has centred chiefly on the B vitamins.

Following on a clue given by Duke-Elder (1954) that large doses of vitamin B_{12} were effective in tobacco amblyopia, even if smoking was continued, my colleagues and I at Bristol (Heaton, McCormick & Freeman, 1958) investigated the serum-vitamin B_{12} levels in tobacco amblyopia. We found that in thirteen patients with the disease the serum-vitamin B_{12} level ranged from 15 to 350 $\mu\mu$g/ml, with a mean value of 218 $\mu\mu$g/ml. The values for twelve controls ranged from 280 to 1000 $\mu\mu$g/ml, with a mean value of 538 $\mu\mu$g/ml. This difference between the patients and the controls was highly significant ($P<0{\cdot}01$).

The commonest cause of a low serum-vitamin B_{12} is histamine-fast achlorhydria. We confirmed Leishman's (1952) findings that just over half of the patients with tobacco amblyopia have histamine-fast achlorhydria. The latter condition sometimes develops into pernicious anaemia and two of our fourteen patients had it; also Leishman (1952) found ten cases of pernicious anaemia among seventy-five cases of tobacco amblyopia.

The condition known as the optic neuritis of pernicious anaemia is probably tobacco amblyopia. Over half of the reported cases were smokers; in the others there was no report of the smoking habits, but the overwhelming majority were males, who are more likely to smoke than females, yet the expected proportion of males to females would be 1 : 3, this being the sex incidence of pernicious anaemia. The field changes and histology in tobacco amblyopia and the optic neuritis of

pernicious anaemia are much the same. This theory explains why the development of amblyopia in pernicious anaemia is not related to the degree of anaemia or neurological involvement and suggests that it is related to the smoking habits of the patient.

The incidence of histamine-fast achlorhydria increases with age, which may be one reason why tobacco amblyopia is commoner in the elderly.

About 40% of patients with tobacco amblyopia have free acid in their gastric juice, so one must look for other causes of their low serum vitamin B_{12}. It is well known that alcoholics often get tobacco amblyopia. Now the vitamin B_{12} metabolism can be upset in these people in several ways. They may be on a poor diet that lacks adequate amounts of vitamin B_{12}. They may have chronic gastritis and enteritis causing their absorption mechanisms to be below par. Finally, they may develop cirrhosis of the liver, and in this condition vitamin B_{12} metabolism is altered; Mackay, Cowling & Grey (1957) suggest that the liver releases a binding protein with a high avidity for vitamin B_{12} and it would 'mop up' any available free vitamin B_{12} and hold it in the blood stream; if it were so there would be less available for tissue metabolism.

Out of fourteen cases of tobacco amblyopia we found that in six liver-function tests gave abnormal results. None of these patients had a history of heavy drinking, however. The total serum-vitamin B_{12} level in these six patients ranged from 15 to 300 $\mu\mu$g/ml, with a mean value of 213 $\mu\mu$g. Unfortunately we were unable to differentiate the free from the combined form.

Diabetics are more liable to develop tobacco amblyopia than normal people, which would be expected as they have an altered vitamin B_{12} metabolism. The so-called diabetic optic neuritis is probably the same condition as tobacco amblyopia, as the majority of victims are men, who smoke more than women, and the field changes in the two conditions are similar.

An interesting condition which attracted a lot of attention during and just after the 1939–45 war is the optic neuritis found in malnourished people; it was especially common in prisoners in the Far East. The general conclusion seems to be that it was chiefly due to a deficiency of one or more of the B vitamins. Vitamin B_{12} had not been isolated at that time so its role was not discussed. Looking back I think it is fair to suggest that deficiency of vitamin B_{12} and smoking played a part in the loss of vision that these people suffered from. Many of them had a central scotoma only, which characterizes vitamin B_1 deficiency; but others had centro-caecal or central and centro-caecal scotomata; a centro-caecal scotoma, especially if it is horizontally oval with a sloping edge and most easily detected by a reduced stimulus, suggests tobacco amblyopia. It is interesting that two authors, Durran (1946) and Goldsmith (1946), noted that vitamin B tablets did not help these patients much, whereas eggs and meat did; the first contained no vitamin B_{12} whereas the last two are rich sources of it. The exact role that vitamin B_{12} and smoking played must remain speculative, but I think that it would be prudent in future to give malnourished people who have optic neuritis vitamin B_{12} as well as other vitamins and advise them to stop smoking.

The part that smoking plays in the production of tobacco amblyopia is not understood and there are several common misconceptions. It is often stated that only heavy smokers get the disease. It is not so: 0·5 oz of tobacco or ten cigarettes a week are enough to produce amblyopia if conditions are right. Traquair (1930) found a mean weekly consumption of 3 oz amongst his amblyopes with a mean age of 55. However, Edwards, McKeown & Whitfield (1959) found that the average healthy pipe smoker aged 60 smoked 2·6 oz a week; we can therefore say that the average tobacco amblyope smokes little more than his healthy counterpart.

As recently as June this year (Anonymous, 1959) an annotation in the *British Medical Journal* stated that tobacco amblyopia is unknown in cigarette smokers. Subsequently there were three letters to the Journal (Evans, 1959; Cohen, 1959; F. P. E. Smith, 1959) in which three separate instances of cigarette smokers' developing tobacco amblyopia were cited. Traquair (1930) and Schepens (1946) also state that they have seen it in cigarette smokers and I have seen two such cases whose histories will be given later.

It is difficult to understand why pipe smokers are so much more liable to tobacco amblyopia than cigarette smokers. I can only suggest two possible factors. Edwards *et al.* (1959) point out that pipe smoking tends to be an old man's foible, as they found a great decline in the proportion of cigarette smokers and an increase in the proportion of pipe smokers with age; as the serum-vitamin B_{12} level decreases with age (Gaffney, Horonick, Okuda, Meier, Chow & Shock, 1957), amblyopia would be associated with pipe rather than cigarette smoking. The other factor is that cigarette smoking stimulates both the parietal and non-parietal cell components of gastric secretion (Piper & Raine, 1959); it has been demonstrated by Halsted *et al.* (1959) that in gastric hypersecretion the serum-vitamin B_{12} level tends to be raised, which might prevent tobacco amblyopia from developing. I suspect that in pipe smokers there is no stimulation of gastric secretion owing to excessive swallowing of some of the smoked products.

Finally, I would like to describe briefly two case histories of cigarette smokers who developed tobacco amblyopia.

The first was a woman of 54 who smoked twenty cigarettes daily and was a heavy drinker. When first seen she had a visual acuity of 6/12 in each eye and her fields were typical of tobacco amblyopia (Fig. 1). She was normal on neurological examination. Her haemoglobin was 17·2 g/100 ml. Her Wassermann reaction was negative and her blood count, results of liver-function tests and urine were normal. Her serum-vitamin B_{12} was 400 $\mu\mu$g/ml. She was treated as an out-patient with 1000 μg cyanocobalamin twice weekly parenterally and she continued to smoke and drink. In 3 months her vision was 6/6 in both eyes and she was in good health.

The second was a women of 52 who smoked ten cigarettes daily and drank heavily. Her visual acuity was: R 6/12, L 6/9 and her fields were those of tobacco amblyopia. Her haemoglobin was 15·2 g/100 ml and her blood count and urine were normal. Her serum-vitamin B_{12} level was 400 $\mu\mu$g/ml. Unfortunately we could not treat her as she developed delirium tremens and bronchopneumonia and died elsewhere.

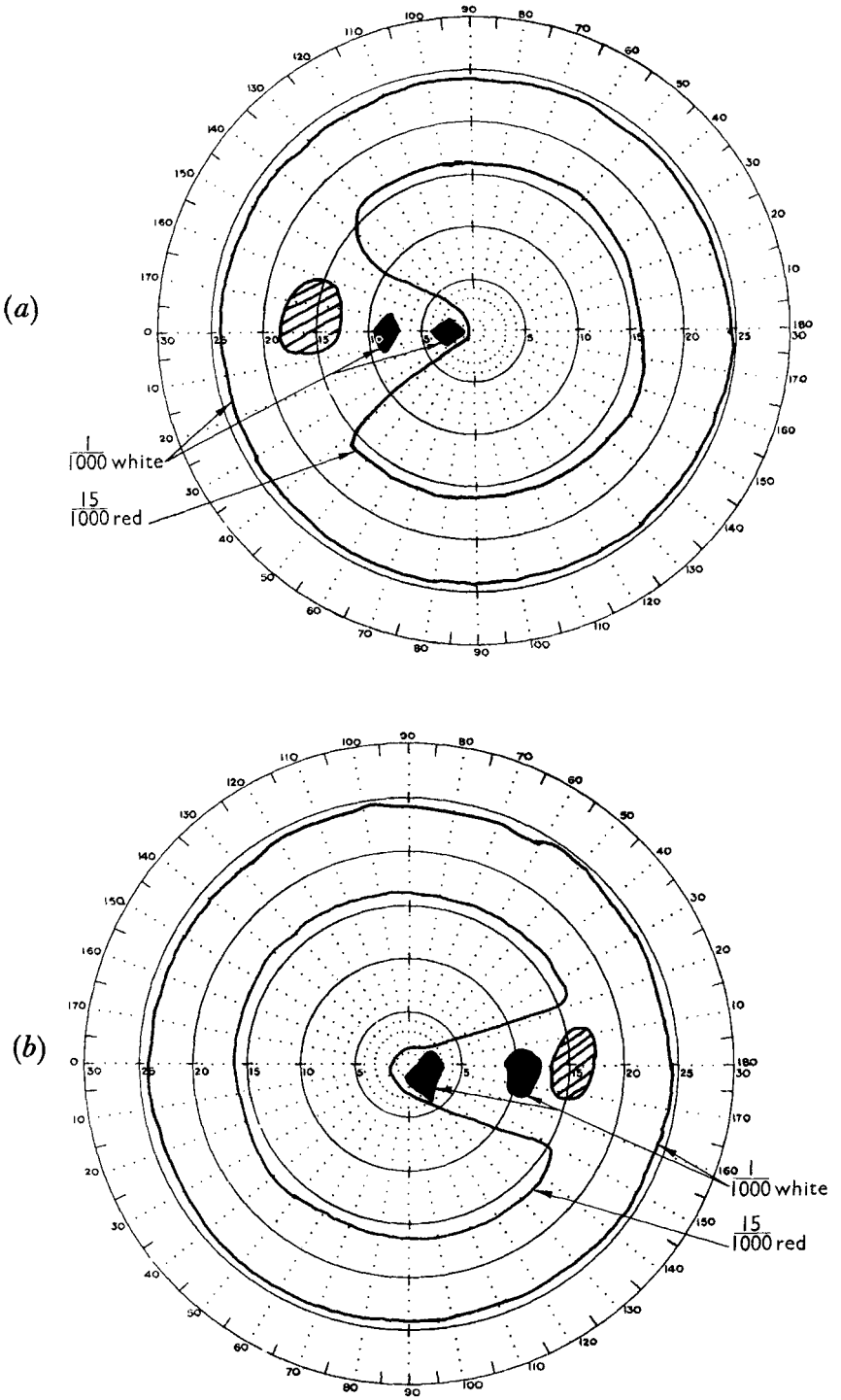

Fig. 1. Tobacco amblyopia field of (*a*) left eye and (*b*) right eye of a woman aged 54 years.

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In these two cases the serum-vitamin B_{12} levels were within normal limits but below the mean for our controls (538 $\mu\mu$g/ml). Although the liver-function tests in the first case gave normal results they are crude tests and there may have been liver damage. Perhaps the relation of free to combined vitamin B_{12} was altered in these patients, so making the retina more sensitive to tobacco.

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