

The toxic optic neuropathies

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WITH

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Contributed by request and dedicated to Sir Stewart Duke-Elder

As is common knowledge, there is an argument as to whether or not the toxic radical cyanide is an important aetiological agent responsible for the development of some of the conditions grouped under the term toxic amblyopia. There are arguments and counter-arguments, and it would appear useful at this stage to state the evidence for and against cyanide as a cause of these conditions.

The argument primarily concerns tobacco amblyopia, but has been enlarged to include certain other conditions including Leber's hereditary optic atrophy and tropical ataxic neuropathy.

In all of these conditions the functional loss is due to demyelination (Sachs, 1887; Rehsteiner, 1930). In tobacco amblyopia the demyelination is restricted to the optic nerve, while in Leber's hereditary optic atrophy it may be more widespread (Wilson 1963).

Early studies showed that cyanide administered to animals could cause demyelination (Hurst, 1942; Lumsden, 1950), and this has been confirmed more recently (Smith and Duckett, 1965; Lessell, 1971). The amount of cyanide needed to cause demyelination, however, is so great that many animals die, while others are made acutely ill. The large dose of cyanide required to cause demyelination in experimental animals is one of the main arguments against cyanide as an aetiological factor in toxic amblyopia, where, apart from the visual loss, there is little other evidence of widespread toxicity.

It is claimed that cyanide is not a cumulative poison and this suggests that chronic exposure to small amounts of cyanide could never result in the accumulation of a sufficient concentration of the radical to cause damage to nervous tissue. When cyanide labelled with ^{14}C is given to experimental animals, however, the labelled carbon does accumulate in the optic nerves (Foulds, Chisholm, and Millar, 1972).

In relation to tobacco amblyopia, there are some who would deny that the condition exists (Potts, 1973), or who consider that, if it does exist, tobacco smoking plays a small part in its production (Silvette, Haag, and Larson, 1960). Some who admit the existence of tobacco amblyopia regard it, at least in part, as a nutritional deficiency disease (Carroll, 1937; Foulds, Chisholm, Brontë-Stewart, and Reid, 1970), and there is good evidence that an improvement in nutrition in those affected may lead to visual improvement (Carroll, 1937, 1944).

As regards the existence of tobacco amblyopia, there certainly exists a group of patients,

usually elderly pipe-smoking men, who exhibit an amblyopia characterized by a bilateral relative centro-caecal field defect, more marked for a red or green target than a white, and who also show a characteristic disturbance of colour discrimination on the Farnsworth-Munsell 100 Hue Test (Chisholm, Brontë-Stewart, and Awduche, 1970). Vision in these patients improves to normal, or near normal, over a period of 3 to 12 months if they stop smoking, and there is no doubt that smoking is one of the factors involved in the production of their visual loss. In our experience, alcohol consumption in these patients is an inconstant factor. Many patients with tobacco amblyopia do drink heavily, but about a third of our patients do not drink at all.

What evidence is there that cyanide is of aetiological significance in toxic amblyopia? We know that tobacco smoke contains a significant amount of cyanide, up to 1,500 parts per million (U.S. Surgeon General, 1964) and that normal smokers excrete significantly increased amounts of thiocyanate, the main detoxication product of cyanide, as compared with non-smokers (Støa, 1957; Pettigrew and Fell, 1972; Pettigrew, 1972). Patients with tobacco amblyopia and those patients with Leber's hereditary optic atrophy who smoke, fail to excrete as much thiocyanate as expected, suggesting an inability to detoxify the cyanide to which they are, undoubtedly, exposed (Wilson and Matthews, 1966; Foulds, Brontë-Stewart, and Chisholm, 1968; Chisholm and Pettigrew, 1970).

The detoxification of cyanide requires sulphur for conjugation with cyanide to produce the harmless detoxication product thiocyanate, and in the human the conversion probably occurs in the liver under the influence of the enzyme Rhodanese (E.C.2.8.1.1.) (Lang, 1933). An inability to detoxify cyanide could, theoretically, result from a lack of a suitable sulphur donor or from a breakdown in the conjugation of sulphur and cyanide.

Is there any evidence that an abnormality of sulphur metabolism occurs in patients with toxic amblyopia? Various aspects of sulphur metabolism can be measured. One of the richest sources of organic sulphur lies in the sulphhydryl group of the tripeptide glutathione. Measurement of red cell glutathione in patients with toxic amblyopia shows that these patients have a significantly lower level of glutathione in the red cells than normal patients (Pettigrew, Fell, and Chisholm, 1972).

An important source of organic sulphur in the body is the sulphur-containing amino-acids, and again a preliminary study of the plasma from patients with tobacco amblyopia shows that they have lower concentrations of the sulphur-containing aminoacids in the plasma than do normal subjects.

Can we relate these differences in sulphur status in patients with tobacco amblyopia to the course of the disease? If patients with tobacco amblyopia, who continue to smoke, are given a sulphur-containing aminoacid by mouth (*e.g.* Cystine 4-8 g. daily) or parenteral inorganic sulphur (Phillips, Wang, and Van Peborgh, 1970), not only does visual improvement occur but there is an increased conjugation of sulphur with cyanide as manifested by an increase in plasma levels and urinary excretion of thiocyanate. In addition, the red cell glutathione level rises.

The biochemical and visual normalization which occurs in patients with tobacco amblyopia when given oral cystine, coupled with the low plasma levels of sulphur-containing aminoacids, suggests that a dietary deficiency of protein may be an important factor in determining the sensitivity to tobacco smoke which these patients exhibit. Our own study on well over 100 patients with tobacco amblyopia suggests that poor diet plays an important role in the development of the condition in at least 30 per cent. of cases. If alcohol is of importance in some cases it may also act *via* dietary protein, for heavy drinkers tend to take a poor diet, which may well be lacking in protein.

The role of vitamin B₁₂ in toxic amblyopia has also to be explained. We know that, although vitamin B₁₂ deficiency, as shown by plasma levels or by whole body radioactive B₁₂ monitoring, occurs in some 30 per cent. of cases with tobacco amblyopia, evidence of defective absorption can be shown in 40 per cent. (Foulds, Chisholm, Brontë-Stewart, and Wilson, 1969).

It is known that patients with tobacco amblyopia, who continue to smoke, will recover vision if treated with large doses of vitamin B₁₂ as hydroxocobalamin but not if given the cyanide-containing form, cyanocobalamin (Chisholm and others, 1967). This improvement in vision is accompanied by an increase in red cell glutathione level and by increased conjugation of cyanide with sulphur as demonstrated by rising plasma levels and urinary excretion of thiocyanate. The changes in red cell glutathione are comparable to those occurring in patients treated with a sulphur donor, such as cystine.

How does vitamin B₁₂ affect sulphur metabolism in this way? In its adenosyl coenzyme form it is required in the elaboration of methionine from homocysteine, and deficiency of vitamin B₁₂ could, at least in theory, interfere with the synthesis of any of the sulphur-containing aminoacids. Thus vitamin B₁₂ deficiency might interfere with the elaboration of a suitable sulphur donor for the detoxication of cyanide. It has already been suggested that protein deficiency may be an important factor in the development of tobacco amblyopia, and patients who are protein deficient are likely also to be vitamin B₁₂ deficient. Their reduced ability to detoxify cyanide might, therefore, result simultaneously from both factors acting together.

In the American literature particularly, the possible role of other members of the B group of vitamins has been stressed. Carroll (1944) showed that recovery of vision in tobacco amblyopia occurred when patients were given B group vitamins. Can members of this group be implicated in sulphur metabolism also?

It is known that several key enzymes in thiol metabolism require pyridoxal phosphate and that their activity is among the first to be lowered by a deficiency of pyridoxine, the biochemical precursor of pyridoxal phosphate. One of them, cystathionase, enables methionine to be converted to cysteine. Lower activity should, therefore, be associated with lowered thiol levels.

We have seen occasional patients with tobacco amblyopia who were folate deficient and not vitamin B₁₂ deficient. Recovery of vision in these cases occurred on treatment with folic acid. Methyl tetrahydrofolate is required with coenzyme vitamin B₁₂ in the elaboration of methionine and, once again, the deficiency could reduce the amount of available sulphur.

If it is agreed that the evidence does at least show that cyanide detoxication is different in patients with tobacco amblyopia from that in normal smoking subjects, how can we explain the neurological lesions which occur? It seems unlikely that they are due to the direct effects of cyanide in view of the known dose-response relationships established for cyanide experimentally.

It is known, however, that, where normal detoxication of cyanide to thiocyanate is faulty, an alternative route may be used leading to the formation of a compound, 2-imino-4-thiazolidine carboxylic acid (Schöberl, Kawohl, and Hamm, 1951; Wood and Cooley, 1956). Recent work on a related carboxylic acid has shown that this substance interferes with the synthesis of choline and consequently, of myelin *via* its inhibitory effect on the re-methylation of methionine from homocysteine, the final step in the biosynthesis of methionine (Lombardini, Coulter, and Talalay, 1970; Gandy, Jacobson, and Sidman, 1973). In the experimental animal, chronic exposure to low concentrations of 1-amino cyclopentane carboxylic acid was shown to cause demyelination, and a similar action is at least

theoretically possible with 2-imino-4-thiazolidine carboxylic acid. It is possible that a compound such as this could, over a period of time, so interfere with the normal turnover of myelin, that areas of demyelination could develop. At present there is little explanation for the localization of demyelination to the papillomacular bundle. The slow recovery of vision which occurs in patients with tobacco amblyopia who stop smoking or who are treated with intramuscular hydroxocobalamin or oral cystine, is compatible with remyelination, which is known to be a slow process when it occurs.

Tobacco amblyopia is, undoubtedly, a rarer condition than formerly and if dietary deficiency of protein is a factor in its development, its increasing rarity is not to be wondered at. In many cases, however, there is no evidence of dietary deficiency, and, in our experience, many of these patients, particularly those whose smoking habits are moderate, show a demonstrable vitamin B₁₂ deficiency.

The relative rarity of tobacco amblyopia means that, in terms of world health, the condition is unimportant. Knowledge of the handling of cyanide under normal and abnormal metabolic conditions is, however, of far-reaching importance in relation to the increasing introduction of cassava as a staple article of diet in tropical and subtropical countries. Cassava is rich in cyanogenetic compounds and is a potent source of dietary cyanide, which has been suggested as the cause of the prevalent severe neurological disease, tropical ataxic neuropathy, which is endemic in areas where cassava forms an important part of the diet (Osuntokun, 1968; Osuntokun, Durowoju, MacFarlane, and Wilson, 1968; Osuntokun, Monekosso, and Wilson, 1969).

References

- CARROLL, F. D. (1937) *Arch. Ophthalm. (Chicago)*, **18**, 948
 ——— (1944) *Amer. J. Ophthalm.*, **27**, 847
 CHISHOLM, I. A., BRONTÉ-STEWART, J. M., and AWDUCHE, E. O. (1970) *Acta ophthalm. (Kbh.)*, **48**, 1145
 ——— (1967) *Lancet*, **2**, 450
 ——— and PETTIGREW, A. R. (1970) *Trans. ophthalm. Soc. U.K.*, **90**, 827
 FOULDS, W. S., BRONTÉ-STEWART, J. M., and CHISHOLM, I. A. (1968) *Nature (Lond.)*, **218**, 586
 ———, CHISHOLM, I. A., BRONTÉ-STEWART, J. M., and REID, H. C. R. (1970) *Trans. ophthalm. Soc. U.K.*, **90**, 739
 ———, ———, ———, and WILSON, T. M. (1969) *Brit. J. Ophthalm.*, **53**, 393
 ———, ———, and MILLAR, W. T. (1972) In "The Optic Nerve, Proc. II Mackenzie Memorial Symposium, Glasgow, 1971", ed. J. S. Cant, p. 270. Kimpton, London
 GANDY, G., JACOBSON, W., and SIDMAN, R. (1973) *J. Physiol. (Lond.)*, **233**, 1 P
 HURST, E. W. (1942) *Aust. J. exp. Biol. med. Sci.*, **20**, 297
 LANG, K. (1933) *Biochem. Z.*, **259**, 243
 LESSELL, S. (1971) *Arch. Ophthalm. (Chicago)*, **86**, 194
 LOMBARDINI, J. B., COULTER, A. W., and TALALAY, P. (1970) *Molec. Pharmacol.*, **6**, 481
 LUMSDEN, G. E. (1950) *J. Neurol. Neurosurg. Psychiat.*, **13**, 1
 OSUNTOKUN, B. O. (1968) *Brain*, **91**, 215
 ———, DUROWOJU, J. E., MACFARLANE, H. M., and WILSON, J. (1968) *Brit. med. J.*, **3**, 647
 ———, MONEKOSSO, G. L., and WILSON, J. (1969) *Ibid.*, **1**, 547
 PETTIGREW, A. R. (1972) In "The Optic Nerve, Proc. II Mackenzie Memorial Symposium, Glasgow, 1971", ed. J. S. Cant, p. 237. Kimpton, London
 ——— and FELL, G. S. (1972) *Clin. Chem.*, **18**, 996
 ———, ———, and CHISHOLM, I. A. (1972) *Exp. Eye Res.*, **14**, 87
 PHILLIPS, C. I., WANG, M. K., and VAN PEBORGH, P. F. (1970) *Trans. ophthalm. Soc. U.K.*, **90**, 809
 POTTS, A. M. (1973) *Surv. Ophthalm.*, **17**, 313

- REHSTEINER, K. (1930) *v. Graefes Arch. Ophthalm.*, **125**, 14
- SACHS, TH. (1887) *Arch. Augenheilk.*, **18**, 21.
- SCHÖBERL, A., KAWOHL, M., and HAMM, R. (1951) *Chem. Ber.*, **84**, 571.
- SILVETTE, H., HAAG, H. B., and LARSON, P. S. (1960) *Amer. J. Ophthalm.*, **50**, 71
- SMITH, A. D. M., and DUCKETT, S. (1965) *Brit. J. exp. Path.*, **46**, 615
- STØA, K. F. (1957) "Studies on Thiocyanate in Serum". Medisinsk rekke no. 2, University of Bergen Årbok 1957
- U.S. SURGEON-GENERAL (1964) "Report on Smoking and Health": Report of the Advisory Committee of the Public Health Service (P.H.S. Publication No. 1103), U.S. Dept. of Health, Education and Welfare, Washington, D.C.
- WILSON, J. (1963) *Brain*, **86**, 347
- and MATTHEWS, D. M. (1966) *Clin. Sci.*, **31**, 1
- WOOD, J. L., and COOLEY, S. L. (1956) *J. biol. Chem.*, **218**, 449