Chronic Cassava Toxicity

Proceedings of an interdisciplinary workshop

Editors: Barry Nestel and Reginald MacIntyre
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Cyanide and Human Disease

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Abstract There is only circumstantial evidence linking human disease with chronic cyanide exposure, although there are many papers describing a variety of neuropathological changes in experimental animals.

The diseases which have so far been considered to result from abnormal detoxication of cyanide (mostly derived from tobacco smoke) are: retrobulbar neuritis in pernicious anaemia; tobacco amblyopia; subacute combined degeneration of the cord in vitamin B₁₂ deficiency; Leber’s hereditary optic atrophy; and dominantly inherited optic atrophy.

In the first condition the abnormal sensitivity to cyanide may be conditioned by acquired vitamin B₁₂ deficiency. In Leber’s disease an inborn metabolic error may prevent mobilisation of sulfur-containing substrates for thiocyanate formation. In dominantly inherited optic atrophy, the metabolic basis is not known, but there is an abnormally high concentration of cyanocobalamin present in the plasma of most patients.

While it is acknowledged that in the ataxic neuropathy of West Africa the aetiology is probably multifactorial, heavy exposure to cyanide or cyanogens from cassava may be particularly damaging in the nutritional context of lack of protein and riboflavin.

Résumé Nous n’avons que des preuves indirectes que l’exposition chronique au cyanure cause des maladies chez l’homme, bien que plusieurs travaux décrivent les changements neuropathiques provoqués expérimentalement chez des animaux.

Les maladies qui, jusqu’à présent, ont été considérées comme résultant de la désintoxication anormale du cyanure (provenant surtout de la fumée de tabac) sont: névrite rétrobulbaire associée à l’anémie pernicieuse; amblyopie causée par le tabac; dégénération combinée subaiguë de la corde associée à une déficience de vitamine B₁₂; atrophie optique héréditaire de Leber; et atrophie optique à caractère héréditaire dominant.

Dans le premier cas, la sensibilité anormale au cyanure peut être conditionnée par une déficience acquise de vitamine B₁₂. Dans la maladie de Leber, un dérangement métabolique inné peut empêcher la mobilisation de substrats contenant du soufre vers la formation de thiocyanate. Dans le cas de l’atrophie optique à caractère héréditaire dominant, on en ignore le principe métabolique, mais la plupart des patients possède une concentration anormalement élevée de cyanocobalamine dans le plasma.

Tout en reconnaissant l’aspect multifactoriel probable de l’éthiologie de la neuropathie ataxique en Afrique occidentale, l’exposition chronique au cyanure ou à des cyanogènes provenant du manioc peut être particulièrement dommageable dans le contexte nutritionnel d’une déficience de protéines et de riboflavine.
EXAMINATION of the medical literature for direct evidence of disease resulting from chronic cyanide exposure is disappointing.

The heavy exposure to volatile cyanide that still sometimes occurs in the metal-refining industry, in metal-cleaning, and in certain photographic processes is variously reported as causing headaches, weight loss (with curious preservation of appetite), and lassitude. It has also been suggested that some Chilean ore-refining workers have developed a clinical picture resembling Parkinson’s Disease, but it is not clear if the patients in question had, in fact, been overcome and partially asphyxiated. The bulk of the evidence I will review is, therefore, indirect and highly circumstantial. It is based largely on demonstrating an association between certain diseases and presumed cyanide exposure either to free hydrogen cyanide (in tobacco smoke) or to cyanogens (in foods). Under normal circumstances, cyanide from these sources appears to be virtually harmless, reflecting the efficiency of the metabolic pathways of detoxication.

Certain experimental studies in the 1930s and 1940s explored the possibility that disturbances in cyanide metabolism might cause human demyelinating disease, notably multiple sclerosis, and as models these studies were not without merit (e.g., Ferraro 1953; Meyer 1933; Rubino 1935; Jedlowski 1937; Jervis 1937; Hurst 1940, 1942; Hicks 1950; Lumsden 1950). Various focal and diffuse lesions of both white and grey matter were produced in a number of different species, but it is extremely difficult to be sure if these were the direct or indirect effects of cyanide. In some of the experiments animals were manifestly asphyxiated, whereas in others relatively large amounts of unbuffered alkaline salts were given parenterally. The interest in cyanide toxicity in multiple sclerosis has never been revived.

In the late 1950s when it was recognised that visual failure in vitamin B₁₂ deficiency occurred predominantly in males, and they were invariably smokers (Heaton et al. 1958), Wokes (1958) suggested that in view of the suspected metabolic interrelationship between cyanide and vitamin B₁₂, the causal factor in smoking was probably cyanide. This hypothesis was extended to include tobacco amblyopia, a clinically similar syndrome, in which plasma vitamin B₁₂ levels are significantly lower than normal, but are not usually in the grossly deficient range (Smith 1961).

Subsequently, Wilson et al. (1971) showed that in the latter condition there is an abnormal increase in the proportion of cyanocobalamin in plasma but not to the extent suggested by Smith (1961). Chisholm et al. (1967) demonstrated that not only do symptoms remit on treatment with large doses of vitamin B₁₂, but that hydroxocobalamin is therapeutically much superior to cyanocobalamin. It has been suggested that tobacco amblyopia and retrobulbar neuritis in pernicious anaemia may result either from a relative block in cyanide detoxication from absolute vitamin B₁₂ deficiency, leading to a damaging accumulation of cyanide (Wilson and Matthews 1966), or from the conversion of one of the physiologically active forms of vitamin B₁₂ to a physiologically inactive form (Smith 1961). I will discuss the relative merits of these hypotheses later.

Concurrently with the interest in the role of cyanide in the pathogenesis of visual disturbance in vitamin B₁₂ deficiency, I became interested in a rare neurological disease known as Leber’s hereditary optic atrophy. This curious malady presents as a more or less severe visual failure occurring acutely or subacutely in males, usually in their late teens. Damage to the central fibres in the optic nerve is usually severe and the blindness permanent. In some patients, there is evidence of other diffuse damage to the central nervous system. Eighty-five percent of European and American patients with this condition are male, and this observation together with the age of onset suggested that smoking might be an environmental factor precipitating the clinical manifestations of an inborn metabolic error (Wilson 1963). This prompted a study of thiocyanate concentrations in body fluids, revealing that the increment in thiocyanate concentration seen in normal smokers compared with non-smokers, is reduced in Leber’s disease, and suggested an abnormality in the conversion of cyanide to thiocyanate (Wilson 1965) (Fig. 1). Moreover, more recent studies of plasma cobalamins showed an abnormal increase in plasma cyanocobalamin concentration not only in patients, but also in clinically affected carriers (Wilson et al. 1971). Not all patients are smokers. One of my cider-loving patients developed his symptoms quite dramatically when he went holidaying in a Sussex village deliberately chosen because it is the place where so-called vintage cider is brewed. His bibulous vacation terminated abruptly and having travelled there on a motor scooter he had to return to London by train be-
cause he could not see. Another patient, also a non-smoker, developed her symptoms following a flare-up in a chronic urinary-tract infection due to _Pseudomonas pyocyanea_, a microorganism known to produce large amounts of free cyanide.

Some of our control samples for our study of cobalamins in Leber’s disease were obtained from patients with another hereditary ophthalmological disease—dominantly inherited optic atrophy—which is clinically and genetically quite distinct from Leber’s disease. This disease usually manifests itself first about the age of 5 years, and is not obviously associated with tobacco smoking. To our surprise, cyanocobalamin levels were also abnormally elevated compared with normal subjects, and this was independent of smoking habits (as in Leber’s disease). It is possible, therefore, that this disease may also represent the clinical effects of an inborn metabolic error of cyanide and/or vitamin B$_{12}$ metabolism.

**Vitamin B$_{12}$ Deficiency**

Human vitamin B$_{12}$ deficiency usually occurs as the result of a failure of vitamin B$_{12}$ absorption from the gut. The principal manifestation is a macrocytic anaemia of varying severity, known as pernicious anaemia, usually accompanied by a conspicuous loss of appetite. In a small minority of patients there is evidence of diffuse disease of the spinal cord and peripheral nerves, known as subacute combined degeneration (SACD). There is an interesting dissociation between the degree of anaemia and severity of the neurological disease. Another interesting feature is the differing sex-incidence.

The male to female ratio in patients with uncomplicated anaemia is 1:2.5, but in patients with SACD the ratio is 1:1.8. The relative excess of males is made up of smokers. In an attempt to explain these observations—the dissociation between the degree of anaemia and SACD, and the excess of smokers with SACD—Langman and I proposed what I still consider is a very neat hypothesis (Langman and Wilson 1966). We suggested that the metabolic equilibrium between thiocyanate and cyanide maintained normally thus:

![Diagram of metabolic equilibrium between thiocyanate and cyanide](image)

**Fig. 1.** Conversion of cyanide to thiocyanate; conversion to 2-aminothiazoline 4-carboxylic acid; incorporation into 1-C pool.

Vitamin B$_{12}$ being essential for the incorporation of cyanide into the single carbon unit metabolic pool. Two further factors operated, according to our hypothesis. First, the reduction in appetite diminishes the amount of thiocyanate ingested (e.g. milk, beer, _Brassica_) and, second, and in parallel, reduces the intake of dietary folate, which in turn increases the severity of the anaemia. This in turn affects the cyanide concentration in the plasma indirectly because we presumed that the activity of the red-cell enzyme, so-called “thiocyanate oxidase” (Goldstein and Rieders 1951, 1953) was dependent on total red-cell mass. We now know that thiocyanate oxidase activity is a property of free haemoglobin and its derivatives.

We studied this relationship prospectively, and
the results were published recently (Wells et al. 1972; Table 1).

These results do indeed support the suggestion that thiocyanate intake parallels folate intake, but go no further. If our hypothesis is correct, the data suggest that variation in red-cell mass is more important than variation in thiocyanate concentration in determining cyanide concentration. Analysis of all our data does, however, show that there is a direct relationship between haemoglobin concentration and thiocyanate level. The one outstanding observation in this study which confirmed our earlier studies was the relationship between smoking and SACD.

The crucial evidence lacking from this and all other laboratory studies is data on cyanide concentrations. Unfortunately, none of the techniques of plasma cyanide assay is really satisfactory for the ultra microassay of free cyanide. All techniques depend on an initial deproteinisation and do not therefore differentiate bound from free cyanide, and the latter is probably metabolically active. Cyanide ions are so very active chemically and have a potent inhibitory effect on such a wide variety of enzymes, that in my view it would seem likely that the pathological consequences are due to direct enzyme inhibition.

Summary

It is acknowledged that this evidence for the role of cyanide in human neurological disease is still very indirect but no more circumstantial, perhaps, than those studies relating smoking to cancer of the lung. Since much of the evidence, however, is concerned with a relationship to smoking (except in the case of dominantly inherited optic atrophy), it could be argued that the abnormalities in cyanocobalamin concentration are merely an indirect index of excessive tobacco smoke exposure. I think this is an unlikely explanation. Likewise, I do not think the hypothesis of vitamin B12 inactivation is tenable since, even in the heaviest smoker with either vitamin B12 deficiency or Leber's optic atrophy, there is no chromatographic evidence of a preponderance of cyanocobalamin, much less total conversion. The biggest stumbling-block at present is the failure to demonstrate either an absolute increase in the concentration of free cyanide in body fluids or an enzyme block in those genetically determined diseases where it is reasonable to expect one.

References


<table>
<thead>
<tr>
<th>Clinical group</th>
<th>Sex</th>
<th>Smokers or non-smokers</th>
<th>Mean plasma thiocyanate concentration (µmole/100 ml ± SD)</th>
<th>Mean haemoglobin concentration (g/100 ml ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Uncomplicated pernicious anaemia</td>
<td>M</td>
<td>F</td>
<td>9.2 ± 1.9</td>
<td>6.9 ± 2.2</td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>F</td>
<td>9.6 ± 5.0</td>
<td>7.4 ± 1.3</td>
</tr>
<tr>
<td>2 Dementia and vitamin B12 deficiency</td>
<td>M</td>
<td>S</td>
<td>5.4 ± 2.0</td>
<td>9.3 ± 2.8</td>
</tr>
<tr>
<td>3 Subacute combined degeneration</td>
<td>M</td>
<td>F</td>
<td>5.0 ± 1.8</td>
<td>11.3 ± 2.5</td>
</tr>
<tr>
<td>4 Folate deficiency</td>
<td>M</td>
<td>S</td>
<td>6.0 ± 3.3</td>
<td>10.6 ± 2.9</td>
</tr>
<tr>
<td>5 Combined controls (groups 5, 6, and 7)</td>
<td>F</td>
<td>NS</td>
<td>4.4 ± 1.7</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>S</td>
<td>S</td>
<td>9.9 ± 4.0</td>
<td>–</td>
</tr>
</tbody>
</table>

*Mean plasma thiocyanate concentrations respectively 4.2, 4.6, and 4.3 µmole/100 ml in non-smoking normal controls (group 7), coronary thrombosis patients (group 6), and elderly medical controls (group 5). Concentrations respectively 10.1, 9.6, and 9.9 µmole/100 ml for smokers. Statistical comparison of mean thiocyanate concentrations (t-test): Group 8 (NS) vs group 4 (NS) P < 0.001; group 8 (S) vs group 1 (S) P > 0.05; group 8 (S) vs group 3 (S) P < 0.01; group 1 (NS) vs group 3 (NS) P > 0.05.


