Ascorbic acid and nitrosamines

EDGAR[1] has proposed that ascorbic acid might inhibit the carcinogenic action of nitrosamines and other carcinogens that may act by alkylation. The rationale was that ascorbate might be alkylated *in vivo* before the carcinogens can react with cell macromolecules. The experimental basis for Edgar's thesis was the statement by Kamm *et al.*[2] that ascorbate inhibited the liver necrosis induced by dimethylnitrosamine (DMN). This statement, however, was presented without experimental details and was subsequently withdrawn[3].

The main concern of the study by Kamm *et al.* was the inhibition by ascorbate of the liver toxicity induced by oral administration of aminopyrine plus nitrite. This study followed our report in 1972 suggesting, on the basis of *in vitro* experiments, that ascorbate might be used to block *in vivo* formation of N-nitroso compounds from nitrosatable chemicals (for example, drugs), since ascorbate efficiently reduces nitrite[4]. Subsequently, the report by Kamm *et al.*[4] appeared. Greenblatt[5] found similar results in mice to those of Kamm *et al.*, but stated that ascorbate did not affect DMN toxicity. We found that ascorbate prevented liver damage from gavage of dimethylamine plus nitrite to rats and, from experiments presented in detail, that ascorbate did not significantly affect the production by DMN of liver necrosis and elevated serum transaminase levels[6]. Ascorbate did not affect transplacental carcinogenesis in rats by ethylnitrosourea, but inhibited carcinogenesis by ethylurea plus nitrite[7].

We are concerned that our original suggestion should not be extended without basis to the hypothesis that ascorbate might have a much wider inhibitory action on carcinogens. The interesting suggestion of Edgar is not supported by the results reviewed here, which were mostly made public after Edgar's paper was submitted.

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● *Nature* regrets that when this article was first published (**250**, 684; 1974) it contained certain typographical errors which may have caused confusion.

Scrapie

IN a group of Herdwick sheep genetically selected for susceptibility to subcutaneous injection with SSBP/1 scrapie brain pool, Pattison reported[1] the occurrence of two cases in uninjected animals. He concluded ". . . that these two cases arose spontaneously by genetic selection". The simplest explanation of these two cases, however, is that they were due to infection with scrapie from some unrecognised source with later cases resulting from lateral and maternal transmission of the infection.

The factual parts of Pattison's report are in accord with our own findings. Cheviot sheep have been selected successfully for increased or decreased susceptibility to scrapie[2,3] following subcutaneous injection with the same source of agent as that used by Pattison. These Cheviot sheep were bred on a geographically isolated farm, away from known cases of scrapie and for the first 7 yr no natural cases of scrapie occurred. Since 1968, however, when a natural 2-yr-old case occurred in the positive selection line, the incidence of natural cases has built up as shown in Table 1, and 81 of the 83 cases have occurred in the positive line. The other two cases have occurred recently in a group of 11 positive-line × negative-line crosses born in 1970. As in Pattison's cases these natural Cheviot cases are easy to distinguish on histological criteria. Because many different strains of scrapie agent can be recognised by the characteristic type, severity and distribution of brain lesions which they produce[4], the histological difference found in the sheep is direct evidence that no component of SSBP/1 is involved in the natural Cheviot cases and this is supported by a failure so far to isolate from them either 22A, 22L or 22C (three strains of agent known to be present in the SSBP/1 pool[5]).

The simplest explanation for the occurrence of the natural Cheviot and Herdwick cases is that the necessary conditions for the total 'isolation' of a flock from direct or indirect contact with scrapie agent are not yet understood. This is not surprising in view of the well known extreme resistance of scrapie agents to physical or chemical inactivation. Also, Icelandic evidence supports the view that there can either be long term persistance of scrapie infectivity on farms in the absence of sheep or that some vector is involved (ref. 6 and P. A. Palsson and B. Sigurdsson, unpublished). Quite apart from these considerations scrapie is known, quite definitely, to be naturally transmitted both laterally and maternally in field conditions (refs 7 and 8 and J. L. Hourrigan *et al.*, unpublished) and among housed sheep[9-12].

One comment is fundamental: it should not be assumed that the Herdwicks and Cheviots which are susceptible to peripheral injection with SSBP/1 scrapie will be susceptible to all strains of scrapie or that the resistant lines will be resistant to all strains. Such an assumption is at the basis of Pattison's interpretation. The situation is clearly illustrated by work with scrapie in mice where it is not possible to describe one genotype as susceptible and another as resistant unless the strain of scrapie agent, dose of agent and route of infection are specified[13].

Although the work with the Cheviot sheep is less advanced than that in mice, there is evidence that a similar situation applies in both species. Pattison cites his own report of scrapie infectivity being produced from apparently normal mouse tissue: these results were interpreted by him as evidence for spontaneous generation of scrapie infectivity ('unmasking')

Table 1 Incidence (%) of natural scrapie in two lines of Cheviot sheep selected for susceptibility (positive line) or resistance (negative line) to subcutaneous injection with SSBP/1 scrapie brain pool

Year born		1957–60	1961–65	1966	1967	1968	1969	1970
Foundation stock		0	—	—	—	—	—	—
Selection line	positive	—	0	1	7	37	23	39
	negative	—	0	0	0	0	0	0

The flock size varied from 120–200 ewes and there were approximately equal numbers in the two selection lines.