Letters to the Editors

Polyols, breath hydrogen and fermentation revisited

I should like to thank Storey and coworkers for their reply (Storey *et al.* 1994) to my Letter to the Editors entitled 'Polyols, breath hydrogen and fermentation' (Livesey, 1994), which referred to their earlier paper on 'Breath hydrogen after ingestion of the bulk sweeteners sorbitol, isomalt and sucrose in chocolate' (Lee *et al.* 1994). The point discussed is the interpretation of breath H_2 responses (BHR) in terms of the extent of fermentation of polyols and bulk sweetener consumed by humans. Attention had been drawn by me to the published evidence that interpretation of BHR is difficult because of differences in the stoichiometry of H_2 production from various carbohydrates and because interactions between carbohydrates affect the overall stoichiometry during anaerobic fermentation both *in vitro* and *in vivo* (Livesey *et al.* 1993). The different stoichiometries and interactions severely limit the use of BHR as an index of the extent of carbohydrate fermentation, particularly when comparing different carbohydrates. Storey *et al.* replied also mentioning other reasons that need to be considered when interpreting *in vivo* H_2 'production' data.

In their reply, emphasis was given to a proposal that breath H_2 production is useful as a tool to overview the extent of digestion and fermentation when used in conjunction with information relating to the incidence of intolerance symptoms. The Nutrition Council of the Netherlands also once considered information on the incidence of intolerance symptoms as an expedient method of assessing availability, although later the Life Sciences Research Office (1994) reviewed and considered this approach, and the BHR approach, not to be reliable for quantification of digestion and fermentation. Substrate intolerance had been used by the Dutch only because of an absence of other information. Attention is drawn to a need for new, more reliable, methods to address problems of nutrient–microorganism interactions in a previous Editorial in this Journal (Gurr, 1990), which also states that 'approaches used are fraught with methodological difficulties and problems of interpretation that were hardly acknowledged by the authors'. Alternative methods and difficulties of interpretation when assessing the availability of carbohydrates to micro-organisms *in vivo* have been reviewed (Livesey, 1994), including a dual stable isotope method in humans which is now being developed further at the Institute of Food Research.

It is interesting to see Fig. 1 in the reply of Storey and co-workers which shows differences in H_2 'production' by faecal micro-organisms *in vitro* when exposed to various sugar alcohols. They compare these data with those published by us (Livesey *et al.* 1993); however, the two data sets are not strictly comparable. To comment on the possible stoichiometry of fermentation one has to suppose that sugar alcohols are fermented completely during the time period shown by Storey *et al.* (1994). Additionally, one must suppose that H_2 'production' expressed as a concentration (ppm, as in their Fig. 1) can adequently represent a production rate (such as kJ H_2 per kJ substrate fermented, as in our studies). With these assumptions their Fig. 1 would show just what is expected on the basis of our previous observations: that H_2 production stoichiometry is high for lactitol and sorbitol and low for isomalt and maltitol. Unfortunately, no information is given on the disappearance of these sugar alcohols during the H_2 'production' shown in Fig. 1 of their reply, nor on whether the H_2 concentration value is a good surrogate for the rate of H_2 production, and so it is difficult to conclude that our findings have been confirmed.

Two factual errors appear in the letter of reply by Storey *et al.* (1994). First, they state that our *in vitro* data on H_2 production are for 168 h of incubation. This is incorrect; as

clearly stated, the time was 12 h (see both the first sentence of text under the heading *Hydrogen production in vitro* and Table 1 in Livesey *et al.* 1993). Second, their reply states that our observation on the low H_2 production from isomalt is based on an incubation of the substrate once only, but it is actually based on information from six incubations (Fig. 4 in Livesey *et al.* 1993), each being either isomalt or mixtures of isomalt with other carbohydrates, some of which had been examined separately in additional incubations. This is a much more sophisticated and informative approach than replicate incubations of substrates presented singly. Moreover, we did not have to repeat our work 14 times (cf. Fig. 1 of Storey *et al.* 1994) to obtain a result in which we could be confident. The similarity of comparable *in vivo* and *in vitro* data in our study (Livesey, 1993), including the interactions, gives further confidence in our results. It is not surprising, therefore, that our data are more reliable than Storey *et al.* would seem to have readers believe and, not surprising also, therefore, that their data are consistent with our own findings. Indeed, no more than consistent because, as explained above, the information they show is too incomplete to confirm our findings.

The key point in my earlier letter and previous publication is that breath H_2 data (and *in vitro* H_2 data) give unreliable quantitative information about the extent of fermentation when comparing different substrates because of differences in stoichiometry. This seems not to be fully acknowledged since Storey *et al.* (1994) state only that 'We would not disagree', but afterwards '... our [Storey's] data from the *in vitro* faecal fermentation studies confirm that isomalt appears to be inherently less fermentable than some other sugar alcohols such as lactitol and sorbitol'. The only new information they supply is H_2 concentrations in faecal incubates *in vitro*, which makes no such confirmation apparent. By contrast, evidence points to all three of these sugar alcohols being completely fermentable (Livesey, 1992; Livesey *et al.* 1993) with differences in stoichiometry of fermentation explaining the differences in H_2 production *in vitro* and to a large extent *in vivo* too! (Livesey *et al.* 1993).

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* This correspondence is now concluded (Editor).

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Vitamin A and retinoids

The term 'vitamin A' was defined (IUNS Committee on Nomenclature, 1978) as the generic descriptor for all C_{20}-β-ionone derivatives that exhibit qualitatively the biological activity of *all-trans* retinol. The term 'provitamin A' for the carotenoids giving rise to vitamin A is retained.

Chemically, vitamin A belongs to the 'retinoids', defined (IUPAC–IUB Joint Commission on Biochemical Nomenclature, 1982) as a class of compounds consisting of four isoprenoid units joined in a head-to-tail manner. These recommendations also contain the statement: all retinoids may be formally derived from a monocyclic parent compound containing five carbon–carbon double bonds and a functional group at the end of the acyclic portion (Fig. 1).

The two definitions do not contradict each other. There are, however, certain implications in the words 'vitamin A' and 'retinoids' that should be considered when using the terms.

'Vitamin A' means a group of substances (retinol, retinyl esters, and retinal) with defined biological activities. Further, there are certain metabolites of vitamin A, such as *all-trans*- and *cis*-isomeric retinoic acids, that can perform some, but not all, of the biological functions of vitamin A; they are incapable of being metabolically converted into retinol, retinal, etc. (Chytil, 1984).

Retinoic acid and some of its isomers and derivatives, together with a number of structurally modified retinoids, have been shown to control cell differentiation in many epithelial tissues and to prevent metaplasia (Sporn *et al.* 1976; Bollag & Matter, 1981). Some of these substances are used in the treatment of various types of keratinization disorders. Such compounds cannot substitute for vitamin A; indeed some of them even act as vitamin A antagonists (Law & Rando, 1989; Hanck *et al.* 1991).

The term 'retinoids' is widely employed for this class of compounds. This practice arose from an earlier proposal (Sporn *et al.* 1976) to use the name 'retinoids' collectively for both natural forms and synthetic analogues of vitamin A that are capable of preventing the development of cancer. General usage of this term is, however, misleading for two reasons. First, the customary practice gives the name 'retinoids', which has an agreed definition based on chemical structure (IUPAC–IUB Joint Commission on Biochemical Nomenclature, 1982), to a class of compounds defined by their biological activity. Second, many synthetic members of this class of compounds, the so-called 'arotinoids' (Loeliger *et al.* 1980) or 'retinoidal benzoic acid derivatives' (Frickel, 1984) as well as others, are not chemically retinoids. The contain, e.g., aromatic rings replacing either the basic β-ionone type ring structure or unsaturated bonds of the tetraene side chain of the retinoid skeleton (Fig. 2).

We now suggest that the compounds that control epithelial differentiation and prevent metaplasia, without possessing the full range of activities of vitamin A, should be termed 'retinoate analogues'. Although they are usually called 'retinoids', we discourage their designation by a term that has a defined, but different, meaning.

A new term for the group of substances with such antimetaplastic activities may be

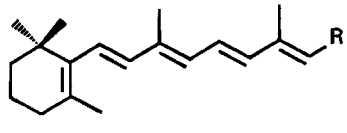

Fig. 1. Structure of the parent compound of retinoids.

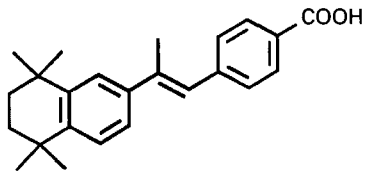

Fig. 2. Structure of an 'arotinoid'.

desirable, especially if it is based on their biological activity. It should not imply a chemical structure because of heterogeneity among the compounds. Proposals for such a term are welcome.

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