Adverse reactions to food additives

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Food additives have had a very bad press. They include a wide range of substances that are added to a food to make it look, taste or smell better or to improve its texture or keeping qualities [1]; so there is no logic in regarding additives as a single group of substances to be randomly condemned. Some could be omitted without difficulty, but food distribution would be seriously threatened without preservatives to prevent bacterial or fungal contamination or without agents that prevent food from deteriorating and becoming rancid. Sulphites are not only preservatives but prevent enzymatic browning in vegetables and fruit. Sodium nitrite inhibits the growth of C. botulinum spores in cured meats. The growth of moulds is prevented by calcium propionate in bread and sorbic acid in drinks.

The merits and disadvantages of each of these substances deserve to be considered separately. To a regulating authority, this means evaluating some 350 antioxidants, colours, preservatives and other miscellaneous additives together with perhaps 3–4,000 flavouring substances. Added to these are contaminants from an early stage of food production, for example pesticide and veterinary drug residues [2], which need to be kept under surveillance.

In the USA, many widely used substances have slowly acquired ‘grandfather status’ (generally-recognised-as-safe). Some also occur naturally. Benzoic acid, which is added to carbonated drinks to prevent microbial spoilage, also occurs in cranberries and a variety of other foods; lecithin, which adds stability to salad dressing and cake mixes, occurs in egg yolks and soya beans; and proteolytic enzymes used, for example, as meat tenderisers are obtainable from papaya (papain), pineapple (bromelain), bovine pancreas (trypsin) and abomasum (pepsin) [3]. In the UK, new additives in the regulated categories must be evaluated extensively for technological need and safety. The position of existing additives is reviewed in response to new information on toxicology, exposure levels, or risk assessments derived from both chemical and clinical information.

Complaints about food additives are chiefly concerned with safety, with the need for ‘cosmetic’ additives such as colours, or with the use of flavouring or bulking agents which disguise or dilute food products. Those who complain, whether they are justified or not, can point to a marked increase in the use of additives between 1955 and 1985 and to an estimate that each person eats 6–11 lb of additives each year [4]. Concerns about food additive intolerance were recently addressed by the European Community Scientific Committee for Food [5], while the Labelling in Food Regulations 1984 set out requirements in the UK for the specific declaration of antioxidants, colouring matter, emulsifiers, stabilisers, mineral hydrocarbons, preservatives, solvents, sweeteners, and a whole host of miscellaneous anti-foaming and anti-caking agents, flavour modifiers (but not flavouring agents as such), flour bleachers and improvers, bulking agents and liquid freezants. By July 1986, all additives had to be listed by name or code number on the wrappers of purchased food; and many members of the public became aware of their presence for the first time. There followed a lively debate about their value and, at least in Britain, particular disdain seemed to attach to code numbers with the prefix ‘E’ (denoting approval by the European Community). When a food company asked housewives if they would buy a product (in fact, spinach) which contained water, vegetable protein and oil, sugars, oxalic acid, colours E140 and E160 and preservatives E250 and E251, many said they would not. The conclusion drawn was that ‘E’ numbers were a disincentive to purchase and, noting this, some manufacturers have substituted seminatural substances such as caramelised sugar. It is questionable whether such policies result in a safer product.

Concern about ‘E’ numbers nevertheless persists, and food labels tend to refer to citric acid and ascorbic acid by name rather than as E330 and E300.

Toxicological data on food additives are widely available to regulating authorities and will not be further considered here. Public concern about additive-induced reactions in susceptible subjects remains, however, at a substantial level. Reports of adverse reactions to additives in medicine [6,7] have also been a cause for comment and are to be the subject of consultations between the Department of Health and pharmaceutical companies [4].

Do additives cause unpleasant reactions?

Suspicions concerning the toxic effects of food additives are not new. ‘Tell your grocer and butcher’, wrote Dr H. W. Wiley in 1913, ‘you will take no more fruits, molasses, sirups or meats that contain sulphurous acid or sulphites’ [8]. It is, indeed, now generally accepted that sulphites can cause asthma [9], and concern has been voiced about a number of other substances. The role of tartrazine in provoking urticaria has been confirmed in double-blind studies [10,11] but its importance has also been queried [12]. The toxic effects of high concentrations of monosodium glutamate have been repeatedly
described [13–15]; and sodium nitrite is reported as causing headache, skin rashes and gastrointestinal symptoms in a dose of 20 mg—within the range that might be encountered in food [16]. Therefore it is necessary to establish that additives are safe in the concentrations in which they are normally used. In practice, this tends to be achieved by establishing a 'no effect' level and then allowing a safety factor of at least ten, with much higher safety factors in some cases [2].

Confirming clinical suspicions

Paradoxically, there has been difficulty in consistently reproducing challenge test results, even in subjects with tartrazine reactions diagnosed by double-blind testing [12]. Even if the initial challenge results are accepted as valid, it appears that the patient's reactivity may wane or disappear, and administration of the challenge material may need to be combined with other circumstances before the reaction becomes manifest. Patients who have immunoglobulin E (IgE) antibodies to foods may fail to react on some occasions but have severe or even dangerous reactions if they take exercise after eating [17,18]. Negative challenge tests in laboratory conditions may not, therefore, be sufficient to exclude an ability to react. In the case of food additives, there are also other factors to consider. The absorption of small molecules is known to rise sharply during bouts of viral gastroenteritis [19] and it may be important to establish whether variations in the absorption of an additive such as tartrazine could also modify an individual's response.

Bearing in mind the vagaries of the clinical response, a number of attempts have been made to increase the reliability of challenge tests by measuring IgE antibodies to foods and food additives or by measuring the release of inflammatory mediators. One outcome has been the demonstration that 'pseudo-allergic' reactions, including urticaria and asthma, frequently present without evidence of an IgE response or of any other immunological mechanism. IgE-mediated reactions to food additives can certainly occur—for example to papain used as a meat tenderiser [20]—but there is evidence of other mechanisms that involve direct toxic effects (eg asthma caused by inhaled sulphur dioxide) or pharmacological effects (eg vasodilatation caused by nitrates). Adverse effects may also be caused by enzyme deficiencies when, for example, the dye orange-RN (prohibited in Europe) is selectively toxic to individuals who lack the enzyme glucose-6-phosphate dehydrogenase [21].

A very similar clinical outcome can thus be triggered by different mechanisms. In place of the search for unidentified immunological abnormalities, increasing efforts have been directed towards obtaining objective evidence of mediator release [22–24] or of a reduced threshold to the non-specific triggering of bronchial reactivity [25].

Estimates of prevalence

When attempts are made to assess the frequency of adverse reactions within a population, there are a number of constraints and difficulties that deserve emphasis [26]. Kerr [27] designed a questionnaire which listed 18 food-associated symptoms, of which three (chest tightness, burning, numbness) were thought to be characteristically associated with the effects of the flavouring enhancer monosodium glutamate. Using this questionnaire, he was able to identify possible cases of the 'Chinese Restaurant Syndrome' among 6.6 per cent of those who answered. When those who had cooperated received a second set of specific questions, including an enquiry about whether they ate in Chinese restaurants and had heard of the adverse effects which can result, the same self-selected respondents gave answers suggesting that in 31 per cent of cases there were adverse effects related to restaurant food. This study highlighted the potential distortions that may follow the use of leading questions. When attempts were made to avoid bias [28], the figures obtained from two further questionnaires were 1.8 and 2.3 per cent.

It remains to be seen whether the 'Chinese Restaurant Syndrome' will prove to be a specific entity or, as has been suggested [29], a non-specific form of oesophageal irritation which could equally well be produced by spiced tomato juice. In either case, prevalence studies are beset by the problems of self-diagnosis and by the difficulty of making adequate allowance for those who do not respond to a questionnaire.

The chief suspects

It has been repeatedly claimed that food dyes, preservatives, antioxidants and nitrates can cause urticaria [30, 31]. Others have found these claims difficult to sustain but accept the probability that tartrazine can provoke urticaria in an occasional patient [10]. In Sweden, where the use of tartrazine has been banned, there does not appear to be firm evidence to indicate what effect this exclusion policy may have had. Convincing evidence is therefore still needed, not only in respect of urticaria but also in relationship to other disorders or behavioural changes attributed to tartrazine and to other food additives.

In the case of sulphiting agents, the results of investigations are less controversial. These substances, when used as preservatives in foods and medicines, have been reported to be capable of causing flushing, throat swelling, itching of the mouth and the skin, and asthma [7, 12, 32]. On the other hand, tests carried out with metabisulphite in capsule form produce no reaction. This material appears to cause problems only when it is in solution [33] and even then may be very difficult to incriminate as the direct cause of a patient's reaction [34]. Allen and Delohery [35] have suggested that solutions of sulphur dioxide (SO2) can be swilled around the mouth with impunity, provided that the test subject holds his breath during the test, whereas, without breath-holding, an identical test can cause asthma. By implication it is the inhaling of SO2 fumes that triggers asthma in such individuals. If confirmed, these findings may help to explain the variable response to a metabisulphite challenge.

With the help of methods such as these, a small number
of potentially harmful substances can now be firmly identified. However, the methods for identifying the adverse effects of additives remain unsatisfactory. Other substances have not been shown to cause clinical problems but are nevertheless the subject of speculation. These include sodium stearyl lactylate in bread, surfactants in juices and coffee creamers, and proteolytic enzymes used as meat tenderisers [36].

**Doubtful clinical syndromes**

Many of the controversies which have arisen about the effects of food additives concern claims that they are a cause of childhood behaviour disorders [37]. While they have often been stated to cause hyperactivity in some children, it is by no means generally agreed that they do so. Most double-blind studies have either given totally negative results [38] or have been largely negative while suggesting that a few, younger children may be better on a restricted diet [39, 40]. Since children who are ill may also be irritable, it is unfortunate that many studies have failed to identify the restlessness and irritability of children with extensive eczema, asthma or rhinitis and to give separate consideration to those whose behaviour problems are unaccompanied by somatic symptoms.

The debate in the UK on food additives is now reaching its peak. In the USA, on the other hand, some investigators have turned their attention to sugar and to yeast [41]. It is notable that in one series, the behaviour disorders of ‘sugar reactive’ children could not be confirmed when the challenge dose was given blind [42]. The link between behaviour and food has yet to be firmly established, but, as noted in a joint Report of the Royal College of Physicians and British Nutrition Foundation [43] the disproportionate publicity it has received is a cause for concern.

**Implications for public policy**

The basis for much of the lobbying against food additives is the belief that, apart from the reactions which a few additives induce in a small number of susceptible individuals, additives as a whole have insidious toxic effects upon the population at large. The strength of this belief is sufficient to encourage the use of unhealthy, obsessive diets for psychologically disturbed children and to stimulate the purchase of unpreserved, aflatoxin-contaminated peanut butter and other foods. Illogical as this attitude may seem, unless more reliable diagnostic tests and toxicological screening methods are developed, there will continue to be members of the public who regard the data as insufficient to give them the reassurance they need.

From the point of view of public policy, a number of specific questions still need to be considered. In seeking to protect the public at large, is it sufficient to label foods and so encourage consumer choice—or are additional measures needed to protect the few who are unusually sensitive? In reviewing the safety of individual additives, what emphasis are we to give to toxicological studies in animals, histamine-releasing and similar properties in human volunteers, the documentation of mild (or severe) reactions in individuals, or the evidence of long-term toxicity? In each of these categories how does the evidence against additives compare with the effects of ordinary foods? Finally, what emphasis should be given to the critical evaluation of additives as compared with public education and advice on healthy eating? Whatever the answers to these questions, the members of the public who are most concerned about food additives may be difficult to convince solely on the basis of conventional medical opinion. This opinion will need to be accompanied by better documented facts.

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Food Intolerance Databank

The series of papers on food intolerance printed in this Journal derive from a research programme initiated by the Ministry of Agriculture, Fisheries and Food after the publication of a joint Report on Food intolerance and food aversion by the Royal College of Physicians and the British Nutrition Foundation. Apart from recommending more research on the prevalence, diagnosis and treatment of food reactions, that Report proposed the setting up of a central databank for food product composition, for the benefit of people intolerant of particular ingredients.

The databank has now been compiled under the auspices of the Food and Drink Federation and is situated at the Leatherhead Food Research Association. It will provide constantly updated information for use by hospital physicians and dieticians. Over 4000 branded products are listed which are free from the ingredients most commonly associated with food intolerance—these ingredients include milk, egg, wheat and soya bean derivatives, cocoa, BHA and BHT, sulphur dioxide, benzoate, glutamate and azo colours.

Organisations which have cooperated in the establishment of the databank include the Royal College of Physicians, the British Nutrition Foundation, British Dietetic Association, Leatherhead Food Research Association, Agriculture and Food Research Corporation Institute of Food Research (Norwich) as well as the Food and Drink Federation and leading UK food manufacturers.