

Michaëlsson G & Juhlin L. Urticaria induced by preservatives and dye additives in food and drugs. *Brit. J. Dermatol.* 88:525-32, 1973.
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Fifty-two patients with recurrent urticaria or angioedema were challenged orally with five different food dyes (tartrazine, Sunset Yellow, New Cocchine, amarant—all azodyes—and Patent Blue), the two preservatives sodium benzoate and 4-OH benzoic acid, and aspirin. Thirty-nine patients developed urticaria; 35 reacted to aspirin; 27, to benzoic acid compounds; and 27, to azodyes; whereas none showed reactions to Patent Blue or placebo. The doses used in the tests could easily be exceeded in daily life by consumption of food and drugs. [The *SCI*® indicates that this paper has been cited in over 155 publications.]

Aspirin and Azodyes Promote Angioedema

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When we started this study, patients with recurrent urticaria were often considered "difficult": time-consuming and requiring the tedious taking of a detailed medical and dietary history, which was often unrevealing with regard to the cause of their urticaria. Usually no relation was found between various food items and the urticarial exacerbations. There was little more to offer than antihistamines. The patient often came back tired and disappointed. Renewed attempts to link seemingly capricious flares to dietary factors were usually unsuccessful.

Some of these patients had abnormal reactions to intradermal injections of kallikrein and prostaglandins. We therefore thought that their urticaria was perhaps mediated not only by histamine but also by other substances and therefore could not be improved sufficiently by antihistamines. However, several patients had normal skin reactions to these vasoactive compounds and still gained no benefit from antihistamines.

It had long been known that patients with recurrent urticaria (and/or bronchial asthma) often have adverse reactions to aspirin. Curiously enough, patients are often unaware of this association. Furthermore, the relevance of the reactivity to aspirin seemed obscure, as many patients with a proven reaction to aspirin were only marginally improved by avoidance of this drug. This puzzled us and prompted us to search for possible hidden dietary or drug factors. Compounds with a structure similar to that of aspirin, as well as other anti-inflammatory drugs, were considered of particular interest. Examples of such substances were azodyes and benzoic acid com-

pounds. Hypersensitivity to the yellow azodye tartrazine had been reported in a few cases of aspirin sensitivity, and when, in a preliminary study, we found that seven-eighths of aspirin-sensitive patients with urticaria and/or asthma had positive provocation tests to tartrazine, our suspicion of the involvement of food additives was strengthened. The large number of reactions to one or several of the azodyes and/or benzoic compounds reported in the cited paper was therefore very encouraging but also surprising.

As a consequence of our findings, we thought patients should be given information on how to avoid these additives. At that time no declarations were given with regard to additives in food and drugs. To help our patients, we had to contact all drug companies and a large number of food industries. Our questions were usually met with interest, and information was obtained, at least from the pharmaceutical companies. The reactions from some international food industries were sometimes negative, with little understanding of our claim that consumers have a right to know the contents of food so that they can avoid components inducing hypersensitivity reactions. Our belief that in the near future the industries would be advertising their products as free from dyes was first met with scepticism but soon became a reality.

An astonishing number of drugs and food products were found to contain dyes and preservatives. No wonder our patients had so many "unexplainable" urticarial attacks and got little help from antihistamines, which were often found to contain azodyes!

One reason this paper has often been cited is probably that it offered a way of taking care of patients with recurrent urticaria. It had been found that these patients often showed substantial improvement if they could stick to a diet free from azodyes and benzoic acid as well as avoid aspirin and other nonsteroidal anti-inflammatory drugs. Our experience at the Department of Dermatology in Uppsala, Sweden, is that the majority of patients benefit from this regimen. In fact, we now advise patients routinely to avoid aspirin, azodyes, and benzoate unless there is some other obvious precipitating cause of their urticaria. For patients with intolerance to aspirin or these additives, it is fairly simple to keep to the diet (as long as they do their own cooking). It does not always solve their problems, however, since cross-reactivity to natural benzoic-like compounds in food and drink is still possible.^{1,2} Although much less than previously, chronic urticaria still remains a problem, since many other hitherto unknown factors are probably also involved.³

Another reason our report is cited may be that it contributed to an increased awareness of hidden agents in food and pointed out the necessity to have them declared. Today this demand seems most reasonable, and a well-developed code system is now being used within the EC [Europeisk Gemensamhet/ European Community] countries for preservatives as well as dyes and many other types of food additives. Furthermore, azodyes are no longer allowed in some countries.

1. Juhlin L, Michaëlsson G & Zetterström O. Urticaria and asthma induced by food-and-drug additives in patients with aspirin hypersensitivity. *Brit. J. Dermatol.* 104:369-81, 1981. (Cited 55 times.)
2. Juhlin L. Additives and chronic urticaria. *Ann. Allergy* 59:1-5, 1987.
3. Czarnetzki B M. *Urticaria*. Berlin, FRG: Springer-Verlag, 1986. 200 p. (Cited 5 times.)

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