

ASPIRIN AND FOOD DYE REACTIONS*

JOHN J. CONDEMI, M.D.

Director, Department of Allergy
Strong Memorial Hospital
Rochester, New York

FOOD reactions as a cause of illness were recognized as early as the first century B.C. by Lucretius, who observed that "one man's meat is another man's poison." Over the subsequent years it has become obvious that this poison may take the form of infection, toxic reaction, pharmacologic (as in the "Chinese restaurant syndrome" due to monosodium glutamate), enzyme deficiencies (such as lactase), and allergic reactions. The word "allergy" was first suggested by Von Pirquet¹ in 1906, but, unfortunately, there continues to be disagreement as to its definition. This had undoubtedly contributed to the confusion concerning adverse reactions to foods and environmental chemicals. The term "allergic" was first used by Von Pirquet to define an "observable altered reaction to environmental substances." By this definition no immunologic mechanism is implied. It should be recognized, however, that when he used the term "allergy" he described the state opposite to immunity. Studies up to that time demonstrated an immune system that protected individuals from the lethal effects of infection, but that on occasion the immune system could result in reaction adverse to the host. The terms that were used to define these adverse immunologic reactions were anaphylaxis (removal of protection) and allergy (meaning a state of altered response).

As the immunologic basis for some of these reactions became more apparent by the use of direct skin tests, passive transfer skin tests, and challenges, a group of physicians, including Hansel, Coca, and, more recently, Rinkel and Randolph, preferred the broader definition of allergy, which did not imply an immunologic reaction to describe adverse reaction

*Presented as part of a course, *Review of Procedures Used in the Practice of Allergy*, presented by the Columbia University College of Physicians and Surgeons and the American Academy of Allergy at the New York Academy of Medicine November 5-7, 1980.
Address for reprint requests: 601 Elmwood Avenue, Box 695, Rochester, N.Y. 14642

to ingested or inhaled material. Fortunately or unfortunately, because these individuals were allergists who diagnosed and treated the usual atopic diseases, they used similar techniques and language to define immunologic and nonimmunologic reactions. They have even suggested that these nonimmunologic reactions be included as type V of the Gell and Coombs classification of allergic diseases. Thus, we can see that as allergy was evolving as a specialty, opinion was divided as to whether allergy should be defined as an altered immune response or just as an altered response. This controversy, unfortunately, has extended beyond the medical community to the public at large. As a result, all of us as physicians are asked our opinions about books written by physicians for the lay public which indicate that "allergies can cause compulsive drinking, depression, compulsive eating, hyperactivity, migraine, asthma, arthritis, chronic fatigue, schizophrenia, hypertension, hypoglycemia, runny nose, clogged sinuses, itchy eyes, eczema, hives, and much more." The authors suggest that patients should "test and treat themselves, take over where their doctors leave off."²

I now find myself in the middle of this controversy by having to discuss the ability of food additives to produce symptoms. It is a controversial subject, not whether such additives can produce adverse reactions, but which ones produce what adverse reactions and how frequently. As a model for these reactions, I have chosen the reaction to acetyl salicylic acid (aspirin) and to food coloring. The first we have all had personal experience with, and the second is based on good control studies documenting behavioral disorders associated with food coloring.

It has clearly been demonstrated that ingestion of aspirin can produce rhinitis, asthma, urticaria, and angioedema. In addition, similar symptoms can be induced in aspirin-sensitive individuals by indomethacin, fenoprofen, naproxen, tolmetin ibuprofen, phenylbutazone, sulindac, tartrazine yellow, other azo dyes, nonazo dyes, sodium benzoate, and parahydroxybenzoic acid. Salicylate-containing foods have also been suggested as a cause of these symptoms, and Feingold³ has also suggested that salicylate-containing foods can also induce behavioral changes in children. These statements, however, have not been documented.

Evaluation of reactions to salicylates and food additives has both advantages and disadvantages. The advantage is the availability of pure chemicals with which to work that can be obtained by any pharmacist. This is in contrast to the complex nature of most foods. Another advantage is that one can estimate how much of these chemicals are available in

TABLE I. ALLOWABLE DAILY INTAKE OF ARTIFICIAL COLORS FOR A 60 KG. PERSON

<i>Color</i>	<i>mg./day</i>
Blue 1	300
Blue 2	37
Green 3	150
Red 3	150
Red 40	420
Yellow 5	300
Yellow 6	300
Orange B	150

an average diet (Table I). This allows some rationale as to maximum amounts to use in testing. Disadvantages are in helping patients avoid food additives for testing and treatment if necessary, and, at the present time, there are no *in vitro* tests or safe techniques to evaluate the role that these agents play in the production of symptoms.

In a patient suspected of a reaction to aspirin, aspirin and all the above noted drugs should be avoided for one week prior to the challenge. A list of aspirin and tartrazine-containing medications is available in a book by Harnet et al.⁴ To determine if patients should be placed on a salicylate food-free diet,⁵ we obtain a salicylate blood level. If any salicylate is detected in the blood we place the patient on a diet; if none is detected, we allow the patient to eat his normal diet. Avoidance of aspirin prior to testing is necessary because a patient who has had a reaction to aspirin may be able to tolerate aspirin without an adverse reaction shortly after the reaction and for several days thereafter.⁶ This refractory period may last seven days. It is interesting that Rinkel described a phenomena known as "masking" in relation to food sensitivity. He suggested that some patients who are sensitive to foods eat such foods frequently or daily to avoid a reaction. He stated that the only way that one can detect this form of food allergy is to have the patient discontinue the food prior to the challenge. He stated that avoidance for a period of four days was necessary prior to the challenge to document the adverse reaction. This obviously is in the range of the refractory period of 3 to 7 days noted for aspirin.

When a challenge⁷ is to be performed for asthma in patients with asthma, they should take all their usual bronchodilators except for cromalin and antihistamines. It is important that the patients have a stable and good (for the patient) timed vital capacity or peak flow recorded prior to the challenge. This is necessary because patients will perform a number of forced expirations, and, if they have airway reactivity, this may be the

basic disease rather than the aspirin sensitivity that induces the drop in vital capacity. Challenges should be performed in the hospital or a hospital setting. Prior to the challenge, the patient has a vital capacity test performed, and is examined. Aspirin is then given, and there is no uniform schedule except that patients should initially receive small amounts of aspirin in order to avoid serious reactions. A fast schedule which has been suggested is that of 30, 150, 300, and 650 mg. of aspirin or a slower schedule of 3, 30, 100, 150, 300, 450, and 650 mg. of aspirin at one to two hour intervals. This can all be given in one day, on subsequent days, or in combination of the two. The classic positive reaction is indicated by a drop in timed vital capacity of over 25% with naso-ocular symptoms. A partial asthmatic response but definite response to aspirin would be a drop in timed vital capacity between 15% and 25% with naso-ocular symptoms. Some patients with a positive response will have no drop in timed vital capacity, but will only develop naso-ocular symptoms; and others will have an asthmatic response but no naso-ocular symptoms.

The aspirin challenge for urticarial reactions can be performed in an outpatient setting as long as the patient has not had a severe anaphylactoid reaction. The challenge should be performed in the morning and antihistamines as well as the previously mentioned additives are avoided. The patient is examined to determine the amount of urticaria that may be present. Challenges are then carried out with 150 mg., 325 mg., and 650 mg. at one to two hour intervals. The patient should be observed for the development of new lesions over the next 24 hours.

If the patient has a reaction to aspirin, then a double-blind challenge should be performed before labelling a patient as aspirin-sensitive. I usually incorporate the placebo challenge with subsequent challenges to sodium benzoate, tartrazine yellow, butylated hydroxytoluene, and butylated hydroxyanisol (A) (Table II). We explain to the patient that we are interested in documenting further the aspirin reaction and in determining whether other food additives are capable of inducing a response similar to aspirin. Capsules containing the above plus a placebo and the amount of aspirin which caused the reaction are prepared. It is important that subsequent challenges be done at least one week after a positive challenge to avoid the refractory period. The cross-sensitivity between aspirin and such food additives as tartrazine yellow, sodium benzoate, and parahydroxybenzoic acid is small (between 1% and 5%, with tartrazine FDA #5

TABLE II. AMOUNTS OF FOOD ADDITIVES
USED IN PROVOCATIVE CHALLENGES

<i>Food additive</i>	<i>mg.</i>
Butylated hydroxytoluene and butylated hydroxyanisol	125/250
Sodium benzoate and parahydroxybenzoic acid	125/250 <i>or</i> 50/100/250
Tartrazine yellow	2.5/5/10/25/50 <i>or</i> 5/25/50
AZO and non-AZO dyes	2.5/5/10/25/50 <i>or</i> 5/25/50

Source: Weiss, B.: Allowable daily intake of artificial colors. Unpublished.

being the most reactive). Cross-sensitivity with nonsteroidal, anti-inflammatory agents is higher, and varying incidences are given from 30% to 90%. The amounts of anti-inflammatory agents used for challenges are shown in Table III. Of interest is that anti-inflammatory agents such as aspirin are prostaglandin inhibitors and will produce symptoms in the same ratio as aspirin. By this is meant that if a patient had a reaction to a small amount of aspirin (such as 40 mg.), he would have a reaction to a small amount of idomethacin (such as 1 mg.) and small amounts of fenopfen and ibuprofen. This type of data has suggested that the common denominator in all these medications is their ability to inhibit prostaglandin synthetase, and any medication with similar properties has the potential for producing a reaction in aspirin-sensitive patients. In our challenges with butylated hydroxytoluene and butylated hydroxyanisol we have noted a rare reaction in aspirin-sensitive patients and a reaction to butylated hydroxyanisol in a nonaspirin-sensitive patient with severe urticaria-angioedema.

In a patient demonstrated to have a reaction to a food additive, the additive is eliminated from the diet. In a patient demonstrated to have a reaction to aspirin and who continues to be symptomatic without aspirin, the patient is offered the opportunity to eliminate salicylate-containing foods from his diet to determine whether symptoms will improve.

The second group of chemicals to discuss is food colors. At the present time, data appear to suggest that food colors can induce behavior changes in children, but the role of food salicylates, acetylsalicylic acid, or food preservatives has not been determined. The initial study⁸ supporting Feingold's suggestion involved 22 children whose parents felt that behavior improved on the Feingold diet. This diet avoids such foods as

TABLE III. AMOUNTS OF ANTI-INFLAMMATORY AGENTS USED IN PROVOCATIVE CHALLENGE

<i>Drug</i>	<i>mg.</i>
Indomethacin	1/5/25
Nefonamic acid	10/50/250
Flufenamic acid	15/150/300
Fenoprofen	15/150/300
Naproxen	10/50/250
Tolmetin	10/100/200
Ibuprofen	20/200/400
Sulindac	10/100/200
Phenylbutazone	5/50/100

almonds, apples, apricots, berries, cherries, currants, grapes, raisins, nectarines, oranges, peaches, plums, prunes, tomatoes, cucumbers, and products made from these foods which are felt to be salicylate-containing foods. In addition, artificial colors, butylated hydroxytoluene, and butylated hydroxyanisole are avoided. In this study, the children were maintained on the above diet and were then challenged intermittently with a blend of seven artificial colors, which included yellow 5, yellow 6, red 40, red 3, blue 1, blue 2, and green 3. The parents' observations provided the criteria of response. Their conclusions were that one child responded mildly to the repeated challenges and one responded dramatically. Swanson,⁹ using larger amounts of the color blend, felt that he was able to induce adverse reactions in 17 of 20 children. The amounts used in all studies were amounts that can easily be ingested in a normal diet. In the latter study, cognitive performance was measured using different doses and a placebo. All of these children had responded to pharmacological management of their behavior but had not been on the Feingold diet prior to the study. The data suggested a dose-response curve with children reacting at different levels, but a peak was reached above which no further increase in reaction could be detected. In all of these studies, the children were on the Feingold diet, and were challenged with blends of the food colors. At the present time one cannot determine whether one dye or all dyes can produce the change of behavior and whether the food colors can produce reactions in adults. In addition, there is no information concerning the role of salicylates or preservatives in inducing behavior changes.

In conclusion, it is clear that acetylsalicylic acid and some food additives can produce adverse reactions that are not produced by sodium or choline salicylate. The types of reactions include asthma, rhinitis, urticaria, and angioedema, and there is a question of their ability to

produce anaphylactoid purpura. Whether salicylates in foods have produced the above symptoms has not been clearly documented. Since food analysis is incomplete, the form and amount of salicylates in foods is difficult to determine. Until this is done, it will be difficult to evaluate the role of salicylates in foods because one will never be sure that the challenge foods contained the salicylate to be tested.

It would also appear that food additives can cause behavior changes. The types of changes will have to be better defined and their extent is to be determined. Whether they occur in adults must also be determined. It is obvious that these reactions are not immunologic and therefore to induce reactions requires larger amounts of the materials than allergists usually use in challenges. It also appears that there is a critical threshold below which patients have no reaction. It is, therefore, important to determine uniform challenge doses and to remain within the amounts ingested by the patient. The mechanisms of the reactions are not known and are described in different ways by different investigators. Some prefer "idiosyncratic" and others prefer "sensitivity" to avoid confusion with allergy. With behavioral changes, those writing in the field now refer to themselves as behavioral toxicologists and the reactions as behavioral toxicity reactions.

With the tremendous interest that our patients have in pursuing the relationship of foods and food additives to their symptoms. I think all physicians should maintain an open mind. We should be working with our patients, allowing them to participate in the investigation of their problems. We should stress the incomplete nature of the evidence and provide experimental guidance to determine if there is any relationship between symptoms and foods. Even if no relationship is found, the patients will appreciate the effort and then may be able to focus on other areas, which may include psychiatric management.

REFERENCES

1. Von Pirquet, and Schick, B.: *Die Serum Krankheit*. Leipzig and Vienna, 1905. *Muench. Med. Wschr.* 53:1457, 1906.
2. Mandell M. and Scanlon, L. W.: *Dr. Mandell's 5 Day Allergy Relief System*. Crowell, 1979.
3. Feingold, B. F.: *Why Your Child is Hyperactive*. New York, Random House, 1975.
4. Harnett, J. C., Spector, S. L., and Farr, R. S.: *Allergy Principles and Practice*,

- Middleton, E. Read, C.E. and Ellis, E.F., editors. St. Louis, Mosby, 1978, p. 1002.
5. Noid, H.E., Schulye, T.W., and Winkelmann, R. F.: Diet plan for patients with salicylate-induced urticaria. *Arch. Dermatol.* 109:866, 1974.
 6. Zeiss, C. R. and Lockey, R. F.: Refractory period to aspirin in a patient with aspirin-induced asthma. *J. Allergy Clin. Immunol.* 57:440, 1976.
 7. Drug Challenge Section IV. *J. Allergy Clin. Immunol.* 64 (6, part 2): 667, 1979.
 8. Weiss, B., Williams, H., Margen, S., et al. Behavioral responses to artificial food colors. *Science* 207:1487, 1980.
 9. Swanson, J.M. and Kinsbourne, M. Food dyes impair performance of hyperactive children on a laboratory learning test. *Science* 207:1485, 1980.