

Asthma caused by FD&C approved dyes

Francis H. Chafee, M.D.,* and Guy A. Settipane, M.D.,**
Providence, R. I.

A case of severe intractable asthma due to sensitivity to certain of the FD&C approved dyes, notably Tartrazine (yellow No. 5), is reported. These dyes are commonly used to color drug tablets and capsules, as well as many foods. Required listing of these dyes on drug and food packages might be life-saving.

Artificial food colors, derived from coal tar and approved by the Food and Drug Administration, have long been suspected to be a cause of urticaria in children who have eaten colored candies. In 1958 Speer¹ reported that artificial colors were the cause of asthma in six children, but gave no further details. A year later Lockey² found that Tartrazine (yellow No. 5), the coloring agent in Decadron, Paracortol, and Deronil tablets, was the cause of urticaria in three adults.

We present in this paper an adult whose severe asthma was caused by certain of these artificial colors.

Case history

Mrs. D. T., age forty-two, was initially seen in 1958. At that time the family history and her past history of allergy were negative. In 1956 she noted the gradual development of chronic nasal blockage and the loss of her sense of taste and smell. She began to wheeze in early 1958, and a diagnosis of infectious asthma was made. Audible wheezing in the chest and evidence of nasal polyposis and sinusitis were the only positive findings of the physical examination. Submucous resection, ethmoidectomy, antrostomy, and excision of nasal polyps were performed, and treatment with a vaccine made from bacterial cultures at the time of operation was instituted. The asthma gradually disappeared under this program.

In January, 1960, her asthma suddenly returned and by the end of the month was only controlled by prednisone. She has had to receive steroid therapy since that time except for

Received for publication Dec. 14, 1966.

*Physician, Consulting Staff, Rhode Island Hospital.

**Assistant Physician, Department of Medicine, and Director, Allergy Clinic, Rhode Island Hospital.

brief periods. The maintenance dose of prednisone has been 5 to 7.5 mg., or its equivalent, daily.

She had to be hospitalized three times during 1962 to control severe attacks. In 1963 she complained of menopausal symptoms which were relieved by a daily dose of Premarin, 1.25 mg. She was hospitalized three times for severe asthma, and at home her symptoms were never truly controlled. It was during this same year that she first was able to describe a tight unproductive cough and a very severe wheezing which was quite distinct from her "usual" asthma.

1964 brought no improvement. In July she took two aspirin tablets for headache, a drug which she often took for this complaint, and within a few moments developed a severe attack of angioedema. She was unable to accept a diagnosis of aspirin sensitivity and, on her own volition, took this drug on two separate occasions. Each time a severe attack of angioedema promptly resulted. She has had no further intake of aspirin, and no further attacks of angioedema. Acetaminophen (Tylenol) was substituted, and one tablet immediately produced severe asthma and the tight, unproductive cough described above. She discontinued all salicylates and antipyretics, but the tight cough and severe wheezing continued. The patient and her physician gradually became aware that this syndrome seemed to be enhanced whenever she took drugs for the relief of asthma, such as, Isuprel-Franol, Elixophyllin, Quibron capsules, or Tedral-25. Antibiotics, such as, Achromycin and Mystecilin-F, seemed to control her infections, but they also definitely enhanced the severe asthma and cough. There was no beneficial response to treatment, and her asthma became increasingly more severe.

In late November, 1964, she was referred to the Pratt Diagnostic Hospital where all medications were stopped. She was discharged a week later, essentially symptom free. Within two weeks the severe asthma returned, and she had to be hospitalized again. The wheezing never truly disappeared during this hospital stay, in spite of bronchoscopy. She was discharged after 3 weeks, only to be readmitted 6 days later, severely ill. She was treated with aminophyllin, hydrocortisone, and fluids intravenously. No oral medications were given. By the sixth hospital day her chest was completely clear, and the tight cough had gone. Hot flashes were her only complaint, so Premarin, 1.25 mg., which had been omitted at the time of admission, was reordered. The tight cough and severe wheeze returned within 3 hours, and continued for 24 hours. Stilbestrol was substituted, the menopausal symptoms were relieved, and there was no return of wheezing. She has had only one attack of severe asthma since her discharge from the hospital in mid-January, 1965, and that attack was on a warm day in May. She had been sitting outdoors near her husband who was applying a lawn fertilizer which contained a fungicide. The severe asthma and tight cough appeared within 2 hours, and, "like the opening of a door," disappeared suddenly 48 hours later. The label showed that the product contained "dimethyl ester of tetrachloroterephthalic acid."

The essential clue that this patient was reacting to something in her medications was revealed by the attack after taking Premarin, and a review of her chart at the preceding hospitalization showed that she had been receiving this drug regularly. When it was learned that Tartrazine (yellow No. 5) was one of its ingredients,³ attention was directed to coloring agents as a possible cause of her asthma.

She continued to do well after discharge. There was some return of the cough after a few days, which was relieved when she stopped the routine use of a vitamin tablet, coated and colored with Tartrazine. From time to time there would be a similar flaring of symptoms, which would stimulate a search for a dye-containing product. Its removal always brought further improvement. The patient wanted to take a vitamin, so Poly-Vi-Sol liquid, a color-free product, was prescribed. Another flare of wheezing promptly recurred, and it was found that the product contained sodium benzoate as a preservative. Other foods containing this chemical were then seen to precipitate attacks, so a search was now directed toward chemical additives. By careful reading of labels, by correspondence with food and drug manufacturers, and by trial and error, a list of food and drugs was finally obtained which was free of FD&C approved coal-tar dyes, sodium benzoate, and drugs derived from coal tar, such as aspirin and acetaminophen. A lipstick was obtained which contained only vegetable dyes. These measures have resulted in complete relief from the syndrome.

At this writing (October, 1966) the patient still has a little morning wheeze which is relieved by a whiff of Isuprel, and she occasionally has some symptoms of sinusitis. The picture is consistent with a diagnosis of infectious asthma. She takes Aristocort, 4 mg. daily, along with a capsule of Premarin, 1.25 mg. This has been especially prepared by the manufacturer and is free of color. She has had no severe attack since May, 1965, and is leading a normal full life.

LABORATORY STUDIES

Extensive laboratory examinations, including bone marrow and electrophoretic studies, were performed during the patient's numerous hospitalizations. The findings were entirely within normal limits, except for a blood eosinophilia of 30 per cent which was found on admission at her last hospitalization. A repeat count the next day was within normal limits. Cultures of the sputum, nose, and throat, repeatedly revealed nonpathogenic flora. Scratch and intracutaneous skin tests to inhalants and foods were also repeatedly negative.

Ouchterlony plate analysis⁴ confirmed the presence of immunoglobulins A, G, and M. Large precipitin bands were observed between the center well, which contained the patient's serum, and the peripheral wells, which contained the separate goat antihuman immunoglobulins, A, G, and M.*

The patient's serum was also analyzed by Ouchterlony plate technique for precipitin antibodies against the dyes. The center well was filled with serum, and each of the peripheral wells contained a 2 per cent solution of one of the FD&C approved dyes. No precipitin bands were seen during a 7 day period of observation.

A double-blind procedure was used to challenge the patient with these dyes. Uniform capsules, colored with vegetable dye, were each filled by a pharmacist with a 2 per cent solution of one of the FD&C approved dyes. Three capsules containing a dye were sealed in each envelope, which the pharmacist then coded. These envelopes were handed to the physician, who, having no knowledge of their content, passed them on to the patient with instructions that she take the contents of one envelope before breakfast every third morning. A record of the reactions was kept, and the code was not broken until after all capsules had been taken. The result appears in Table I.

Patch tests with a 2 per cent solution of each of the dyes were applied to the skin of the patient's upper arm. No local dermatitis nor increase in wheezing was noted within the next 72 hours.

The patient was tested by the skin-window technique.⁵ After cleansing, sites on the volar surface of the forearm were prepared by scraping away the superficial layers of the skin with a sterile scalpel until a sheen of tissue fluid was obtained. A drop of 2 per cent solution of each dye was placed on a separate site which was then covered with a sterile glass cover slip, backed by a cardboard, and bound down with adhesive tape. A drop of normal saline for a control was placed on an additional site and similarly covered. Twenty-four hours later the cover slips were removed, coded, and then handed to a hematology technician. His report is given in Table II.

*Hyland Laboratories, Los Angeles, Calif.

Table I. *Result of oral ingestion of dyes*

<i>Envelope</i>	<i>Capsules</i>	<i>Symptoms</i>
A	Red No. 2	No symptoms
B	Red No. 3	No symptoms
C	Yellow No. 5	Tickling of throat; tight cough and wheezing for 24 hours
D	Blue No. 1	No symptoms
E	Placebo	No symptoms
F	Red No. 4	Little heaviness of chest
G	Yellow No. 6	No symptoms
H	Placebo	No symptoms

Table II. *Eosinophilotactic response to FD&C dyes*

<i>Slide</i>	<i>Dye</i>	<i>Total cells counted</i>	<i>% eosinophilia</i>
A	Blue No. 1	100	9
B	Red No. 2	100	2
C	Yellow No. 5	100	8
D	Yellow No. 6	100	6
E	Saline	4	0

Table III. *Eosinophilotactic response to FD&C dyes by passive transfer*

<i>Slide</i>	<i>Dye</i>	<i>Primed site</i>		<i>Unprimed site</i>	
		<i>Total cells counted</i>	<i>% eosinophilia</i>	<i>Total cells counted</i>	<i>% eosinophilia</i>
P	Blue No. 1	100	3	100	3
Q	Red No. 2	100	1	0	
R	Yellow No. 5	100	44	0	
S	Yellow No. 6	100	25	100	5
T	Saline	100	15		

Passive-transfer testing on a nonallergic male by the same technique was then done. Sites on the volar aspect of the forearm were each primed with 0.10 ml. of the patient's serum 24 hours in advance of the skin scraping. An equal number of sites were also scraped on an area of skin which had not been primed. A 2 per cent solution of each dye was then placed on a primed and also an unprimed site, covered with a sterile glass cover slip, and bound in the usual manner. They were removed 24 hours later, coded, and handed to the hematology technician. Table III contains findings.

Skin-window tests with aspirin, acetaminophen, and sodium benzoate were not done, for it was felt that sensitivity to these substances had been adequately proven clinically.

DISCUSSION

Until mid-1962 the patient's asthmatic symptoms behaved according to the usual conception implied in the diagnosis of infectious asthma. She had chronic wheezing which was not related to environment or season, and which was defi-

nately made worse by respiratory infection. Patients with this disease often develop an aspirin sensitivity, and, when this happened to our patient, we at first considered it to be another manifestation of the disease.

After June, 1962, a new syndrome appeared which was superimposed upon her usual asthma. These symptoms consisted of a markedly tight cough, which was often sudden in its onset, and which was always associated with an unproductive cough and with a severe asthma. She frequently commented that "this asthma is *different*"—a remark with which her physician concurred, but did not know how to interpret. The dramatic reappearance of this syndrome following Premarin at her last hospitalization provided the means for its understanding.

Some drug manufacturers employ vegetable dyes to color their products. Most companies use one or more of the FD&C dyes which are derived from coal tar or petroleum, for they are quite stabile and will not be changed by a long shelf life. The actual dye used in any individual product is a trade secret and will not readily be revealed. We have had cooperation from the medical departments of the companies concerned, when we have asked for the dyes in a specific product and have given the reasons for our request. Even so, it has been a time-consuming procedure. It is difficult for the average physician, and nigh impossible for the patient, to obtain this information. It would be far easier for the physician, let alone the patient sensitive to these chemicals, if the Food and Drug Administration were to require listing of the dyes on the package.

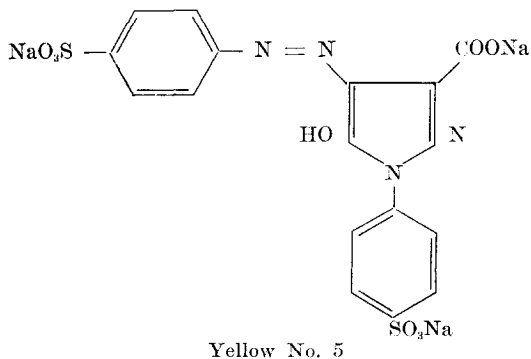
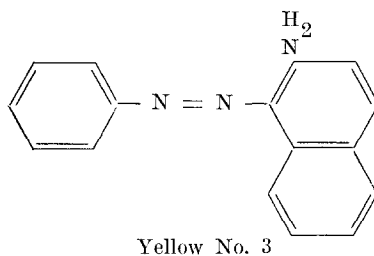
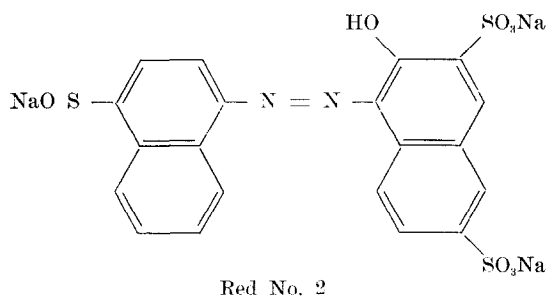
The same comment is applicable to food. These dyes, such as Tartrazine (yellow No. 5), are at times added without being listed on the label and some food manufacturers are loathe to admit that chemicals, other than those required to be listed, are added to their products. Other companies, in contrast, have freely answered our requests for information.

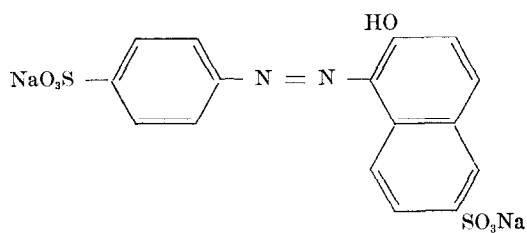
Another possible contact with these dyes occurs in the hospital operating room where solutions—notably of cocaine—are often colored for identification by the hospital pharmacy. Irrigating solutions employed by the ear, nose, and throat surgeon must also be screened. Neither of these is labeled as to dye content.

There are 11 coal-tar dyes which are certified by the Food and Drug Administration,⁶ and 5 of these (red No. 2, red No. 4, yellow No. 5, yellow No. 6, and blue No. 1) are most commonly used. Blue No. 1 was the only dye in one drug which caused symptoms in our patient, and yellow No. 6 was the sole one in another. Both of these dyes gave no response in the double-blind oral test, which might imply that these dyes were poor stimulators of antibody and must be given over a period of time to bring results. Positive results were obtained to each of them in the skin-window procedure on the patient's skin, so antibodies were present, confirming our impression of clinical sensitivity. Eidinger and his co-workers⁷ noted that a less-marked eosinophilic response was usually obtained in the recipient's skin on passive transfer, and Fowler and Lowell⁸ confirmed this finding in their need to prime the sites with larger amounts of serum than usual. This finding might explain the lack of response to blue No. 1 in the skin of our nonallergic recipient. The positive response to yellow No. 6, though, does show that some anti-

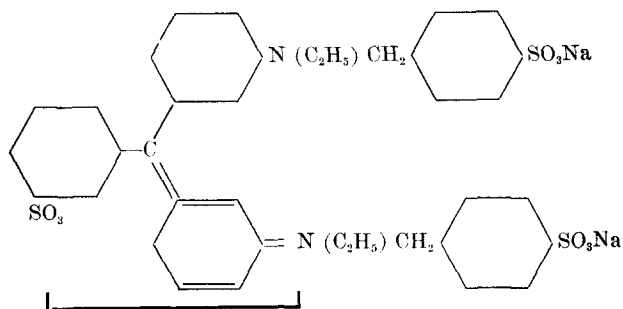
bodies were transmitted in quantity and that it is not always necessary to prime the passive-transfer site more heavily. In the clinical investigation we believed that yellow No. 5 was the most severe offender, and this impression was amply confirmed not only by the positive double-blind oral test, but also by the unequivocal results obtained in the skin-window procedures.

It is, therefore, interesting to speculate upon the possible relationship between her sensitivity and the chemical structure of yellow No. 5, yellow No. 6, aspirin, acetaminophen, sodium benzoate, and the compound of terephthalic acid.^{6, 10}

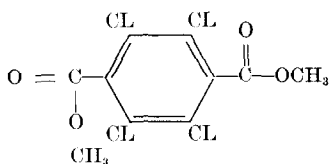




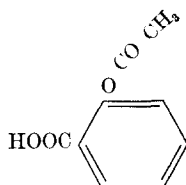
Yellow No. 6



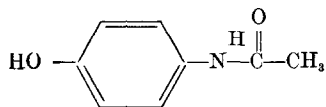
Blue No. 1



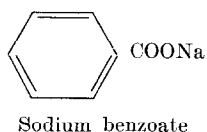
Dimethyl tetrachloroterephthalic acid



Aspirin



Acetaminophen



All of these compounds are aromatic, and some include other heterocyclic rings, such as are found in Tartrazine. They all contain acidic carboxyl or sulfonic acid groups. Our patient apparently had no clinical reaction to yellow No. 3, and, although this compound is aromatic, it is free of acidic groups. The sensitivity to aspirin, sodium benzoate, and acetaminophen may, therefore, be ascribed to the presence of a carboxyl group on an aromatic ring. Her sensitivity to dimethyl tetrachloroterephthalic acid inhalation is explained on the basis of a ready hydrolysis of the methyl ester groups in vivo, thereby giving rise to free carboxyl groups—again on an aromatic ring. It has to be assumed that these reactive acidic groups are somehow involved in a haptene formation,¹¹ and it is not clear why other non acidic reactive groups, such as amino groups, play no part. At any rate, those dyes which contain only sulfonic acid groups appear to be less effective in producing a sensitivity reaction in our case, and no clinical reaction has occurred when our patient has ingested those chemicals which have basic, rather than acidic, groups.

Finally, we should like to give credit for the solution of this case to the patient herself. It can honestly be said that, if it were not for her objectivity and intelligence in observing, interpreting, and reporting of her symptoms, she probably would not be alive today.

REFERENCES

1. Speer, F.: *The Management of Childhood Asthma*, Springfield, Ill. 1958, Charles C Thomas, Publisher, p. 23.
2. Lockey, S.: Allergic Reactions Due to FD&C Yellow No. 5 Tartrazine, an Aniline Dye Used as a Coloring and Identifying Agent in Various Steroids, *Ann. Allergy* **17**: 719, 1959.
3. Jewell, J. B.: Personal Communication.
4. Ouchterlony, O.: Diffusion in Gel Methods for Immunological Analysis, in Kallos, P., editor: *Progress in Allergy*, New York, 1958, S. Karger AG, vol. 5, pp. 1-78.
5. Rebuck, J. W., and Crowley, J. H.: Part II. Techniques in the Study of Leukocytic Functions. A Method of Studying Leukocytic Functions in Vivo, *Ann. New York Acad. Sc.* **59**: 757, 1955.
6. Speer, F.: Food Allergens, in Speer F., editor: *The Allergic Child*, New York, 1963, Harper & Row, Publishers, pp. 106-137.
7. Eidinger, D., Raff, M., and Rose, B.: Tissue Eosinophilia in Hypersensitivity Reactions as Revealed by the Human Skin Window, *Nature* **196**: 683, 1962.
8. Fowler, J. W., III., and Lowell, F. C.: The Accumulation of Eosinophiles as an Allergic Response to Allergen Applied to the Denuded Skin Surface, *J. Allergy* **37**: 19, 1966.
9. The Merck Index, Rahway, N. J., 1962, Merck and Co., Inc.
10. Bukantz, Samuel C.: Personal Communication.
11. Gell, P. G. H., Harington, C. R., and Michel, R.: The Antigenic Function of Simple Chemical Compounds: Correlation of Antigenicity with Chemical Reactivity, *Brit. J. Exper. Path.* **29**: 578, 1948.