

Concerning the nature of intolerance to aspirin

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(1) Intolerance to aspirin is not uncommon in individuals near middle age who, as a rule, do not have a history of atopy. It is characterized by changes in the skin and respiratory mucous membranes—angioedema, perennial rhinitis, formation of nasal polyps, and bronchial asthma—which precede the development of intolerance to aspirin. (2) While reactions induced by aspirin simulate an immunological disease evidence for an allergy to acetylsalicylic acid per se or acetylsalicylic acid as an antigenic determinant is unconvincing. Attempts to demonstrate antibodies to acetylsalicylic acid have been generally unsuccessful. (3) If an immunological etiology can be ruled out, aspirin must induce its effects by a direct action on effector organs. (4) Acetylsalicylic acid can inhibit at least one mediator-induced reflex, i.e., the kinin-induced vasodilatation in the skin of man and the kinin-induced bronchoconstriction of the guinea pig. (5) Patients who have an intolerance to aspirin have a comparable intolerance to other minor analgesics, e.g., pyrazolones and indomethacin. Reactions to these structurally dissimilar compounds occur after first administration. It appears reasonable to assume that they exert their effect on the same receptors. (6) It is proposed that aspirin produces characteristic symptoms in aspirin-sensitive patients by activating peripheral chemoreceptors which have been altered by a pre-existing disease. (7) A possible mechanism by which peripheral chemoreceptors might participate in the pathogenesis of bronchial asthma has been outlined and reviewed in the light of what is known about reflexes which control the vascular bed of the skin and the functional state of the respiratory mucous membranes.

Reports that the ingestion of aspirin can produce severe allergic reactions appeared shortly after the discovery of the drug.¹ Since then, a substantial number of related observations has been published, and their similarity is impressive.² In a recent tabulation, Bruce Pearson³ states that of 1,205 asthmatic patients of all ages on his services, 2.3 per cent were aspirin-

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sensitive, but the incidence increases in middle age: consequently, published statistics vary according to the type of patients who form the basis of the statistics.

By and large, the literature suggests that an immunological mechanism accounts for the peculiar features of aspirin sensitivity, i.e., the acute episodes of acute angioedema or acute and severe bronchial asthma which simulate anaphylaxis. Bruce Pearson states, "It is generally assumed that aspirin acts as a complement and forms an antigen in combination with serum protein," but raises some question about this "mysterious clinical entity." Friedlaender and Feinberg⁴—in a review of 45 aspirin-sensitive patients—comment on the lack of specific skin reactions (in spite of the severity of symptoms), record a sensitivity to drugs other than aspirin in 13 patients, and conclude that "repeated exposure to other substances of a chemical nature, also incapable of giving positive skin tests, may be responsible for the chronic asthma encountered in these individuals. Allergy to aspirin may be an indicator that the individual acquired the mechanism to react to simple chemical compounds." Feinberg concluded that in the absence of positive skin reactions the antibody with which aspirin reacts must have been induced by an extraneous antigen which has not been identified⁵ but might include infectious agents, bacterial toxins, and products of tissue breakdown; indeed, aspirin sensitivity has been classified as a form of infectious asthma.

It has been known for some time that aspirin-sensitive patients are able to take sodium salicylate with impunity, but, even in the absence of reactions to sodium salicylate, it is conceivable that a specific immunological sensitivity to acetylsalicylic acid exists.⁶ In spite of numerous attempts, however, it has not been possible to demonstrate the existence of unequivocal antibodies to acetylsalicylic acid: most of the studies so far either report antibodies to salicylates or permit alternate interpretations.⁷⁻¹²

BRIEF COMMENTS ON THE NATURAL HISTORY OF INTOLERANCE TO ASPIRIN

Intolerance to aspirin is not uncommon. From 1954 until 1965, we have followed more than 1,000 aspirin-sensitive patients who suffered from angioedema, rhinitis, and/or bronchial asthma; of these, 182 were hospitalized for intensive study.

The initial manifestation of the disease which is eventually associated with intolerance to aspirin is a vasomotor rhinitis, distinguished by profuse watery secretion, which develops in the majority of patients during the second or third decade, is at first intermittent, later perennial, and commonly followed by the formation of nasal polyps.

Bronchial asthma in aspirin-sensitive patients tends to occur in middle age. Precipitating factors are rarely defined, but nasal polypectomy seems to bring on the first attack of bronchial asthma in a suggestive number of patients. In the beginning, the bronchial obstruction is readily reversible with isoproterenol; and even later, bronchial asthma of aspirin-sensitive patients often can be controlled with surprisingly low maintenance doses of corticosteroids.

Many authors believe that bronchial asthma of aspirin-sensitive patients is invariably progressive and has a much higher mortality rate than bronchial asthma in general; statistical evaluation of our own group, however, makes us believe that the over-all prognostic picture is better than the literature suggests.

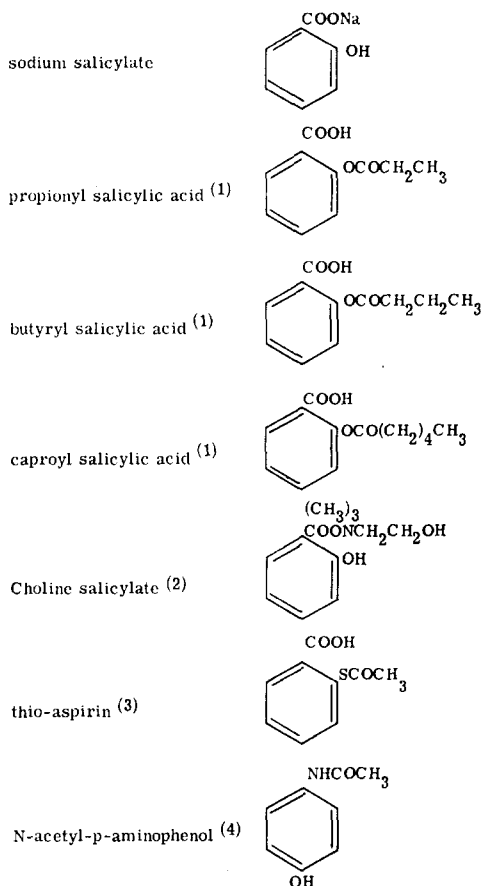
Intolerance to aspirin is not the cause of the disease. In the majority of our patients, respiratory symptoms precede the development of intolerance to aspirin, often by years; and religious avoidance of aspirin and aspirin-containing compounds by patients with established intolerance to aspirin does not, as a rule, alter the natural history of the disease, i.e., recurrence of symptoms and progression.

In contrast to surveys published by others, the incidence of atopy in our group of patients is low: only about 3 per cent of our patients had a personal history of atopy—compared with an expected incidence of atopy of at least 10 per cent, but probably significantly higher,¹³ in any unselected group of the population—but the incidence of atopy in their offspring is substantial and reasonably close to the expected figure. We do not wish to imply that the relative absence of atopy in our group argues against a possible immunological mechanism, but it seems curious that the incidence of atopy in our patients is so much lower than one would expect.

THE SPECIFICITY OF INTOLERANCE TO ASPIRIN

In order to clarify the biochemical spectrum of intolerance to acetylsalicylic acid, each of the patients under our care received (a) sodium salicylate and (b) one or several of the compounds which are listed in Figs. 1 and 2. The compounds include (1) salicylic acid esters with lengthening side chains, (2) choline-salicylate, (3) thio-aspirin, (4) acetyl-p-aminophenol, (5) diacetylfluorescein, and (6) Trasentine-azo-salicylate. Propionylsalicylic acid behaves *in vitro* like aspirin: it is hydrolyzed by the cholinesterase of washed red blood cells and of serum. Diacetylfluorescein is a white, nonfluorescent powder, but deacetylation produces brilliant fluorescence in minimal doses; consequently, the compound lends itself well to studies of gastrointestinal absorption, since onset and degree of deacetylation can be readily established by fluorometric analysis. Thio-aspirin and acetyl-p-aminophenol are not deacetylated either *in vivo* or *in vitro*. None of these compounds induced any symptoms in aspirin-sensitive patients.¹⁴

Extensive *in vitro* studies which we have carried out in recent years have failed to uncover any fundamental differences in the handling of acetylsalicylic acid by various test systems, e.g., plasma and red blood cells obtained from aspirin-sensitive patients and normal controls. In essence, the studies confirm the information which has been summarized in several excellent monographs in recent years.¹⁵⁻¹⁷ *In vitro* binding of sodium salicylate and acetylsalicylic acid by serum proteins is the same in aspirin-sensitive and non-aspirin-sensitive patients. The rate of deacetylation is the same in serum from aspirin-sensitive patients and from normal controls; and red blood cells obtained from aspirin-sensitive patients and normal controls deacetylate acetylcholine

**Fig. 1**

Compounds tolerated by patients with established intolerance to acetylsalicylic acid. (1, Prepared for us by Dr. C. S. Marvel, The William Albert Noyes Laboratory, Department of Chemistry, and Dr. E. C. Taylor, Jr., Department of Chemistry and Chemical Engineering, University of Illinois, Urbana, Ill. 2, Supplied as Arthropan by Dr. Harry S. Tirsch, The Purdue Frederick Company, New York, N. Y. 3, Synthesized by Drs. M. L. Tainter and C. M. Suter, Sterling-Winthrop Research Institute, Rensselaer, N. Y. 4, Supplied as Apamide by Dr. Max Gilbert, The Ames Company, Elkhart, Ind.)

at a comparable rate (methods used: Saltzman,¹⁸ Trinder,¹⁹ Hofstee,²⁰ and Michel²¹).

In vivo absorption of sodium salicylate and acetylsalicylic acid varies greatly from one individual to another but is reasonably constant within the same individual. Separation of bound and unbound salicylate by equilibrium dialysis showed no difference in the handling of sodium salicylate by aspirin-sensitive and non-aspirin-sensitive patients. It is not possible, of course, to administer acetylsalicylic acid routinely to aspirin-sensitive patients for experimental studies, but it is of interest that the rate of deacetylation of diacetylfluorescein is the same in aspirin-sensitive and non-aspirin-sensitive patients.

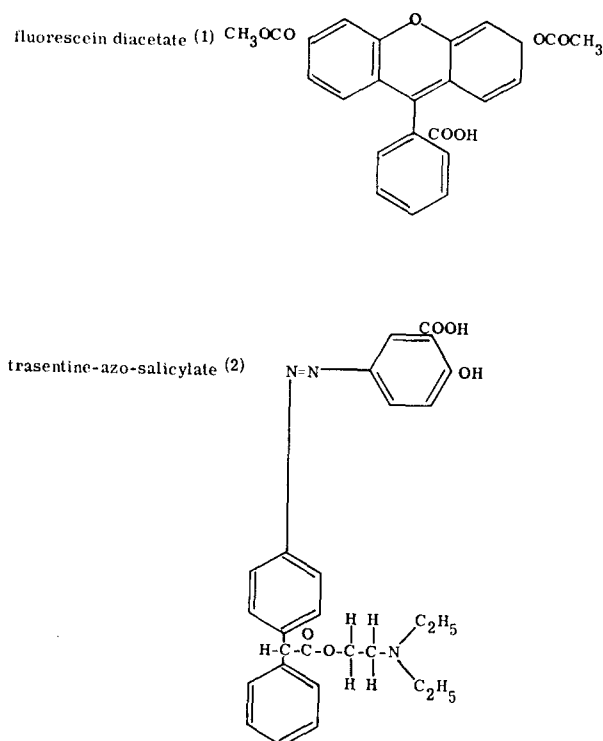


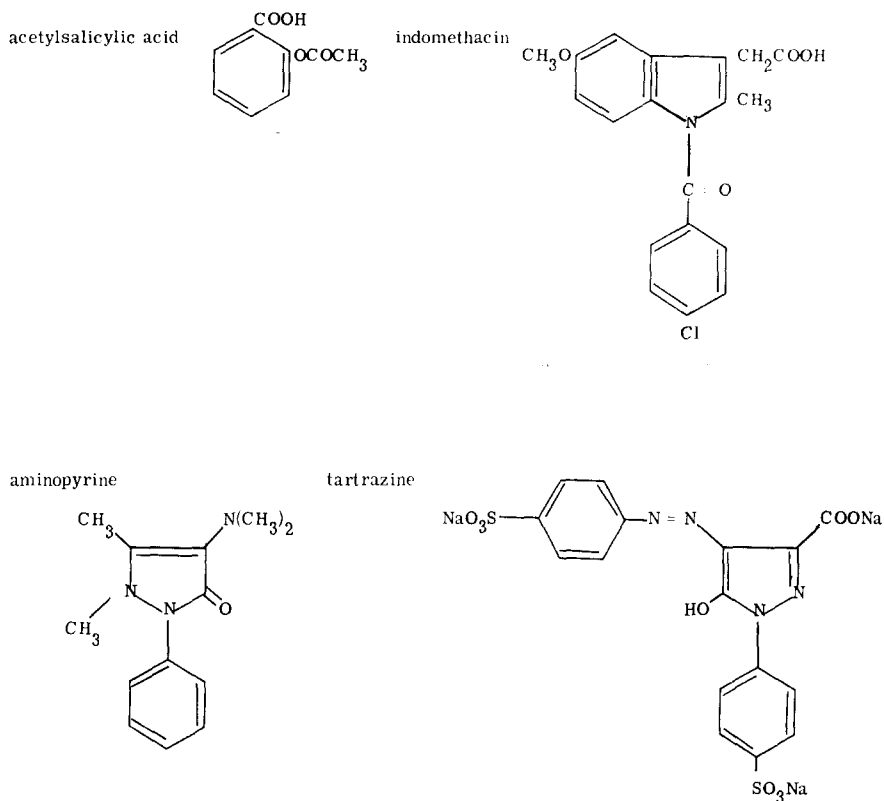
Fig. 2

Fluorescein diacetate and Trasentine-azo-salicylate. (1, Prepared by Dr. R. O. Hauck, Knoll Pharmaceutical Company, Orange, N. J. 2, Synthesized by Patricia G. Sudar, the Graduate College, Chicago Professional Colleges, University of Illinois, 1955.)

REACTIONS TO CHEMICALS OTHER THAN ASPIRIN IN ASPIRIN-SENSITIVE PATIENTS

While intolerance to acetylsalicylic acid is not intolerance to salicylates, a number of chemicals cause rhinitis and bronchial asthma in aspirin-sensitive patients; they are identified in Fig. 3. Aminopyrine (and antipyrine) have been responsible for several severe reactions, but their number is limited because physicians are reluctant to prescribe these drugs. Tartrazine, FD&C yellow No. 5, produced nasal and bronchial symptoms in 9 of our 182 hospitalized patients. During the summer of 1965, we administered 25 mg. of tartrazine in aqueous solution to 80 ambulant and hospitalized patients under rigidly controlled, double-blind conditions. One half of the participating patients were aspirin-sensitive. Only 3 patients reacted to the administration of tartrazine with rhinorrhea and bronchoconstriction, but the 3 reactors were aspirin-sensitive; even so, the low incidence of reactions surprised us.

After we observed, by chance, that indomethacin precipitated bronchial asthma in one of our aspirin-sensitive asthmatics, we have given indomethacin (25 mg.) to 18 hospitalized aspirin-sensitive patients; each of these patients

**Fig. 3**

Compounds which induce reactions in patients with established intolerance to acetylsalicylic acid. (Indomethacin supplied as Indocin by Dr. Gilbert M. Bayne, Merck, Sharp and Dohme Laboratories, West Point, Pa. Tartrazine supplied by Mr. W. H. Kretlow, the Wm. J. Stange Company, Chicago, Ill.)

developed severe bronchial obstruction which required extensive symptomatic therapy.

Since an intolerance to acetylsalicylic acid seems to be associated with an intolerance to pyrazolones and indomethacin, a correlation might exist between the manner in which aspirin, and other minor analgesics, relieve pain and the manner in which aspirin induces nasal and bronchial reactions in aspirin-sensitive patients.

In recent years, it has been shown that the relief of pain by acetylsalicylic acid and by some other minor analgesics involves peripheral as well as central action. Lim and associates²² have offered convincing evidence that aspirin acts by competitive inhibition of chemoreceptors of pain. It appears that bradykinin and related polypeptides stimulate pain receptors; and that certain, but not all, effects of bradykinin can be prevented by pretreatment with acetylsalicylic acid. In man, aspirin abolishes the bradykinin-induced axon reflex, i.e., the vasodilatation considered part of the defenses against various forms

of injury; in guinea pigs, aspirin inhibits bradykinin-induced bronchoconstriction.²³ The assumption that aspirin causes severe reactions in either respiratory tract or skin by direct activation of sensory receptors implies (1) that chemoreceptors of skin and mucous membranes are capable of inducing increased blood flow and increased vascular permeability in skin and mucous membranes, as well as bronchoconstriction and secretion of mucous glands, and (2) that aspirin in an abnormal receptor system might, in aspirin-sensitive patients, activate rather than inhibit peripheral chemoreceptors. It is the objective of this report to examine this postulate.

THE NATURE OF AXON REFLEX AND ANTIDROMIC VASODILATATION

Like histamine, as bradykinin acts on chemoreceptors of the skin, it initiates an axon reflex. Studies of the effects of physical, thermal, or chemical irritation on the vascular bed have been carried out on the skin, and it is generally agreed that a variety of stimuli are followed by antidromic vasodilatation.^{24, 25} Crossland²⁶ describes the pathway of antidromic vasodilatation.

Mild mechanical stimulation of the skin causes vasodilatation in the stimulated area due, it is widely believed, to the operation of an axon reflex. Cutaneous sensory nerves arising from some skin receptors also receive branches from arterioles in the same areas of the skin. Impulses from the receptors travel along the sensory fibers into the cord in the usual way, but in addition as they pass the point where the vascular branches join, they initiate impulses which pass centrifugally in these branches—in the opposite direction, that is, to that normally taken by impulses in sensory nerves—to produce a vasodilator response.*

The nature of the chemical mediator, or mediators, which produce vasodilatation is uncertain. Some investigators believe that the mediator which initiates the sequence of the receptor, e.g., histamine, also elicits the vascular response, but Parrot and Lefebvre²⁷ have shown that antihistamines which inhibit histamine-induced vasodilatation will not abolish vasodilatation elicited by stimulation of the peripheral end of posterior root fibers.

Paton,²⁸ in a thoughtful review of the pharmacology of antidromic vasodilatation, acknowledges that the proper mediators for rapid vascular responses remain to be identified:

But now we know that sensory nerves contain very little histamine or acetylcholine, and since atropine or potent antihistamines do not reduce antidromic vasodilatation, nor (as I have observed myself) the flare response evoked by histamine, one has to seek for other mediators of the vasodilatation. I have speculated whether the vasodilatation seen in blushing may not be partly mediated by the same means. Blushing is usually attributed to a relief of sympathetic tone. Yet the patchiness of it is of a kind that I have not seen in subjects undergoing ganglion block; and the latency is rather short. The other day I asked a laboratory assistant whether he blushed; within a period of about 10 seconds he was scarlet. In contrast, the rise in blood-flow of the forearm in response to heating the feet, which is certainly due to release of vasoconstrictor tone in the arm, appears to take several minutes to develop.†

Of the substances which induce an axon reflex after local application to, or release from within, the skin, histamine has been studied most extensively.

*Crossland, J.: Some Possible Mediators of Non-cholinergic Central Transmission, in Elliot, K. A. C., Page, Irvine H., and Quastel, J. H., editors: *Neurochemistry, the Chemistry of Brain and Nerve*, Springfield, Ill., 1962, Charles C Thomas, Publisher, p. 657.

†Paton, W. D. M.: Pharmacology of Vasodilator Drugs With Special Reference to the Skin, in Rook, A., editor: *Progress in the Biological Sciences in Relation to Dermatology*, London, 1960, Cambridge University Press, p. 429.

It has not been possible, however, to demonstrate the existence of "histaminergic" nerves; and it has not been shown that histamine can be released from nerve fibers by electrical stimulation.

The same general statement holds true for most, if not all, of the chemicals which, like serotonin, ATP, and polypeptides, e.g., bradykinin or substance P, act on chemoreceptors. It is fair to state that the hypotheses which assign the activation of the chemoreceptor and the subsequent antidromic vasodilatation to the same substance have become less and less attractive.

SIMILARITIES BETWEEN REFLEXES IN THE SKIN AND IN THE RESPIRATORY MUCOUS MEMBRANE

In the skin, histamine has been the most widely examined mediator and Ungar, Grossiord, and Brincourt²⁹ have suggested as early as 1936 that histaminergic fibers produce antidromic vasodilatation in the lungs of dogs. In recent years, Aviado^{30, 31} has suggested (1) that histamine induces parasympathetic bronchoconstriction and (2) that parasympathetic stimulation initiates a feedback mechanism which in turn inhibits the release of additional histamine. Aviado suggests that bradykinin might act in a similar fashion, but this suggestion, while attractive, remains to be substantiated by experimental evidence.

It is likely that stimuli which are generated at chemoreceptors of the respiratory mucous membrane not only induce an axon reflex but are carried to the dorsal root ganglion and beyond.³² In other words, bronchoconstriction might represent not only the result of abnormal stimulation of peripheral receptors, but the combined result of exaggerated peripheral responses transmitted to an unduly responsive system of autonomic controls within the bronchial tree.

THE EFFECT OF ASPIRIN ON PERIPHERAL CHEMORECEPTORS

Aspirin acts as a competitive inhibitor for many, but not all, bradykinin receptors. The axon reflex which is induced by topical application of tetrahydrofurfuryl nicotinate (Fig. 4)—thought to release vasoactive kinins—can be effectively inhibited by pretreatment with comparatively small doses of acetylsalicylic acid in normal subjects.³³ Aspirin does not inhibit axon reflexes which are induced by other irritants, including reactions induced by application of histamine and methacholine.³⁴ It is interesting to note that

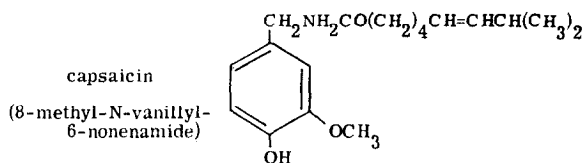


Fig. 4

Tetrahydrofurfuryl nicotinate. (Supplied as Trafuril by Dr. J. H. Fryer, CIBA Limited, Basel, Switzerland.)

aspirin does not abolish the direct effect (e.g., the formation of a wheal) of injected bradykinin, but that aspirin prevents secondary effects, i.e., the axon reflex and the antidromic vasodilatation.

Normally, the chemoreceptors of the nasal and bronchial mucosa are not activated by aspirin; in fact, it has been said that acetylsalicylic acid is a helpful adjunct in the treatment of bronchial asthma.³⁵

In aspirin-sensitive patients, aspirin produces—either immediately or after a latent period which might extend to up to 3 hours—angioedema, rhinitis, and bronchial asthma. We believe that aspirin causes these effects by direct stimulation of chemoreceptors in either skin or nasal and bronchial mucous membrane; and we shall present, briefly, the rationale for this interpretation.

The question arises, of course, why acetylsalicylic acid, an antagonist to kinins, should act as an agonist in aspirin-sensitive patients and initiate rather than prevent stimuli at the site of the chemoreceptor. In recent years, several attempts have been made to clarify the biochemical difference between agonists and antagonists. Paton,^{36, 37} for instance, has proposed a kinetic theory of drug-receptor interaction, applied to acetylcholine and acetylcholine antagonists and, more recently, to adrenergic mediators and receptors. Paton suggests that only the agonist disassociates rapidly; the antagonist forms a comparatively stable complex with receptor protein which prevents short-acting agonists from reaching and stimulating receptor sites. If a pre-existing disease, therefore, would decrease or destroy the capacity of the receptor to bind antagonists, antagonists might be expected to stimulate, rather than to block, receptor sites.

In spite of extensive studies, the relative significance of sympathetic and parasympathetic control in the maintenance of normal bronchomotor tone has not been clearly established; specifically, it appears that results obtained in normal men³⁸⁻⁴⁰ do not necessarily apply to patients with pre-existing bronchoconstriction. Even so, Widdicombe,⁴¹ after a comprehensive review of the existing evidence, concludes, "It is probably wise to accept the conventional view that vagal nerves are constrictor, and sympathetic dilator, to the tracheo-bronchial tree; while remembering that many experiments which indicate that this is an oversimplification have yet to be explained."

Atropine fails to control the aspirin-induced bronchoconstriction of aspirin-sensitive patients; their response to isoproterenol remains intact. While this does not necessarily preclude a possible role of sympathetic and parasympathetic abnormalities in the pathogenesis of the syndrome, it is tempting and, we believe, logical to trace the bronchoconstriction of aspirin-sensitive patients to receptors which have not been previously identified as a cause of nasal and bronchial congestion; and which, like the peripheral chemoreceptors, are equipped for rapid control of the air-conditioning structures of the respiratory tract.

The natural history of what we have called "aspirin disease" suggests that aspirin-sensitive patients develop changes in the chemoreceptors, in the nasal and bronchial mucous membranes, or of the skin, which, at first, result in exaggerated responses to physiological stimulation. After a variable interval, often years after

onset, patients record an intolerance to acetylsalicylic acid. If the responsible receptors are kinin receptors, they should, and would normally, be inhibited by aspirin, but aspirin-sensitive receptors are not normal. If the receptor distortion at this particular moment has progressed to a point where aspirin can no longer form a stable complex with the receptor, it would be no longer an antagonist, but an agonist, and initiate the series of reflexes which we have described.

If intolerance to aspirin is caused by changes in peripheral chemoreceptors, other peripheral analgesics, i.e., chemicals reacting on the same or similar receptors should induce comparable reactions. We have demonstrated that this assumption is correct for (1) aminopyrine (and antipyrine), (2) indomethacin, and (3) tartrazine (FD&C yellow No. 5), which is a pyrazole derivative.^{42, 43} Indomethacin will induce severe reactions in most, if not all, aspirin-sensitive patients, but FD&C yellow No. 5—which is capable of inducing reactions—will induce these reactions only in a certain, comparatively small percentage of aspirin-sensitive patients. It is our impression that tartrazine requires biotransformation before it becomes an effective metabolite, and that this biotransformation occurs only in a limited number of patients under conditions which are currently under study.*

Anti-inflammatory drugs, on the other hand, might not act on the same chemoreceptors: neither phenylbutazone nor 1-(N-methyl-piperidyl-4')-3-phenyl-4-benzyl-pyrazolone-5 induce untoward reactions, and they can be taken with impunity by aspirin-sensitive patients. Consequently, it appears that not only anti-inflammatory drugs and peripheral analgesics differ in their mode of action, but that minor analgesics which induce antidromic responses in aspirin-sensitive patients might differ in their mode of action from minor analgesics which, like N-acetyl-p-aminophenol or sodium salicylate, are tolerated without untoward reactions.

DESENSITIZATION OF CHEMORECEPTORS

Attempts to desensitize hypersensitive peripheral receptors have been made, but have not been very successful. On the basis of Jancso's⁴⁴ studies, we have used the active principle of red pepper, capsaicin, a highly irritating substituted benzylamide of a long-chain unsaturated fatty acid (Fig. 5). Capsaicin sensitizes peripheral receptors,⁴⁵ but has the peculiar ability to desensitize the same receptors on continued application, either topically or by injection. Jancso demonstrated that capsaicin does not only induce nonresponsiveness of chemoreceptors to capsaicin, but also to nicotine and acetylcholine, while the response to physical stimulation is unimpaired.

Desensitization, of course, is not new. Repeated application of nicotine desensitizes to nicotine. Repeated application of acetylcholine desensitizes to acetylcholine, but none of these desensitizes to capsaicin, formalin, and similar

*In a recent study of a patient sensitive to acetylsalicylic acid as well as to FD&C approved dyes, Chafee, F. H., and Settignano, G. A. (*J. ALLERGY* 40: 65, 1967) call attention to the possible importance of free carboxyl groups attached to aromatic rings for the development of symptoms.

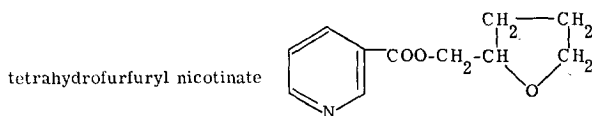


Fig. 5

Capsaicin, the active principle of various species of *Capsicum solanaceae*.

irritants. Desensitization to capsaicin, on the other hand, "... blocks the axon reflexes throughout the body and blocks them permanently."⁴⁶ We are still uncertain, however, whether capsaicin will desensitize not only normal receptors but also the abnormal receptors of aspirin-sensitive patients.

CONCLUSIONS

In the absence of convincing evidence that acetylsalicylic acid is an antigen or an antigenic determinant (except under in vitro conditions which have no relation to the clinical syndrome) it seemed desirable to examine alternate explanations for the severe reactions which it produces in selected patients. Our assumption that aspirin acts directly and paradoxically on peripheral chemoreceptors has been strengthened by the recognition that other, chemically unrelated, peripheral analgesics produce identical symptoms on first exposure. The possible role of altered components of the autonomic nervous system in the pathogenesis of bronchial asthma⁴⁷—with particular emphasis on the vagus⁴⁸⁻⁵⁰—has been debated for many years, but none of the theories which have been offered has wholly explained the natural history of bronchial asthma. Investigation of the normal and abnormal behavior of peripheral chemoreceptors might provide a missing link and a better understanding of the nonspecific factors which determine the course of a specific disease.

Intolerance to aspirin has some features which we cannot understand at present, e.g., the etiology of nasal polyps or the meaning of the eosinophilia which tends to be associated with the syndrome. Even so, we feel justified in proposing that aspirin-induced reactions are the result of a receptor disease which requires further study and clarification.

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