Some Observations On Food Allergy

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ALLERGY includes a group of human disease reactions caused by a specific and exaggerated sensitiveness toward substances which are usually harmless. Acquaintance with some of the fundamental concepts of this subject has become important to the food manufacturer, because allergic disturbances due to foods occasionally simulate symptoms of food poisoning of various types. Pain sensations or violent gastro-intestinal disturbances suggestive of caustic poisons, bacterial toxins or other contaminants are now recognized among the many manifestations of allergy.

Allegations of personal injury attributed to contaminants in foods can be validated or invalidated by chemical and bacteriological examination. Identification of the cause of allergic disturbances, however, depends solely upon clinical procedures which have not attained an especially high degree of precision or uniformity. Evaluation of clinical evidence, therefore, becomes the only means of determining whether observed allergic disturbances can be properly attributed to a particular dietary item and whether discrimination against a particular food can be justified by a calculable frequency of allergic reactions due alone to the suspected food.

An historical approach to the subject of allergy avoids the difficulty of defining its content and limits, a feat not yet accomplished with universal satisfaction. This approach also provides for an understanding of an unfortunate confusion in terminology which has resulted from the rapid advance in clinical applications of the theories concerning specific sensitiveness in the lower animals and man.

The current doctrines of allergy include several conflicting theories with respect to the physiological basis of disease reactions which result from hypersensitiveness. This special branch of clinical medicine is an outgrowth of animal experiments dealing with one of the most spectacular phenomena of biology—the anaphylactic shock. Early investigators of the methods for establishing immunity to disease noted that occasionally repeated injections of an immunizing substance resulted in sudden and unaccountable death of an experimental animal.

Portier and Richet (1) originated the name anaphylaxis (without protection) and applied it to this phenomenon to denote a condition of increased susceptibility and to contrast it with increased protection (prophylaxis) which was the usual result from repeated injection of an immunizing substance. The anaphylactic reaction in experimental animals was intensively studied and these fundamentally important facts were established: An experimental animal, such as the guinea pig, will tolerate without apparent effect a first injection of a soluble foreign protein—that is, a soluble protein derived from a plant or an animal of another species. During an interval of several days or weeks following the first injection the animal develops a specific sensitiveness to only that protein which was first injected. A second injection of the same protein will thereafter cause an immediate violently toxic physiological reaction, an anaphylactic shock, which generaly results in the death of the animal within a few minutes after the second injection.

Anaphylaxis is characterized as a specific hypersensitiveness to a foreign protein, established during an interval of several days following a first injection of the protein. The manifestations of the anaphylactic shock differ among different species of animals and proteins vary with respect to their capacity to accomplish the anaphylactic reaction. Most important characteristics of this condition are the high degree of specificity exhibited by the sensitized animals toward a particular protein and the astounding potency of the protein in anaphylactic sensitizing and shocking reactions. For example, a guinea pig will tolerate without harm several cubic centimeters of the blood serum of a horse upon first injection, but will suffer a fatal shock from a second injection of as little as 0.01 cc. of the same protein. Investigators determining the minimum quantity of protein required to accomplish anaphylactic sensitization in the guinea pig have reported positive results with 0.000,001 cc. of blood serum of the horse and with 0.000,05 mg. of crystalline albumin of the hen's egg. Chemists have found the anaphylactic reaction so specific that this biological response is a most dependable method for differentiating between proteins which are as similar chemically as the egg albumins from the duck and the hen. It may be noted at this point that the allergic reaction in the human often possesses these same characteristics of specificity and the phenomenal toxic potency of minute doses of protein.

Apparently, no disease symptoms in the human were recognized as being analogous to experimental anaphylaxis in the animal until 1906 when Wolff-Eisner (2) suggested that hay fever in many might be an anaphylactic reaction. Four years later Meltzer (3) pointed out a notable similarity between the paroxysms of asthma in man and the respiratory climax of the anaphylactic shock in the guinea pig. He concluded that asthma was not due to functional disorder of the nerves as was the current belief, but was in reality an anaphylactic response to a foreign protein to which the asthmatic patient had become sensitized. Evidence supporting the theories of Wolff-Eisner and Meltzer accumulated rapidly and clinicians soon found that many other clinical forms of idiosyncrasy displayed by the human could be explained on the basis of specific sensitization to proteins derived from the environment or diet. The term anaphylaxis came into general use with special qualifications, such as food anaphylaxis, alimentary and cutaneous anaphylaxis, to denote the source of the specific excitant or site of the manifestations and human hypersensitiveness.

Important differences were noted, however, between experimental anaphylaxis in the lower animals and a varied group of disease reactions in the human which were being rec-

ognized as anaphylactic disturbances. The need for a term to identify all clinical reactions of this order seemed to be satisfied by von Pirquet's "allergie," which he had coined (4) to denote simply "die veränderte Reaktionsfähigkeit . . . "altered reaction capacities," to be applied with restrictive qualifications of causes or symptoms.

Unfortunately, the term allergy did not long retain the meaning assigned to it by von Pirquet. In 1913, Doerr (5) classified under this term several distinct types of biological phenomena conditioned by either an increased or a decreased susceptibility to specific agents. Other investigators vigorously protested the integration in meaning of both anaphylaxis and allergy, and their indiscrimnate application to significantly different experimental and clinical manifestations of specific sensitiveness. The result of much debate upon this subject was the introduction and use of the term hypersensitiveness and atopy to designate some of the same conditions and reactions in the human which were being identified by clinicians as allergy or more rarely as anaphylaxis.

When the Journal of Allergy appeared in November, 1929, an editorial announcement in the initial issue recognized the need for justifying the selection of this title. Conceding that the term allergy did not possess an established meaning in scientific usage, the editorial explained that the term was employed in the title of this Journal in accordance with current medical usage among clinicians who recognized as allergy conditions of specific hypersensitiveness, exclusive of anaphylaxis in lower animals. In this sense allergy became the generally accepted designation for any human manifestation of exaggerated physiological sensitiveness without exacting consideration of the chemical or physical nature of the specific excitant or the means by which it might become effective in the human.

Allergy appears to be the term preferred by the majority and allergen is generally applied to those allergenic substances or agents which excite allergic disease by some unknown specifically reactive mechanism in the allergic patient.

When diagnosis of disease reactions incriminates a particular kind or class of food there arises the question of determining whether the suspected food is at fault because of contamination or whether the reported disease reactions are manifestations of allergy. Diagnosis of the disease response is a clinical problem and is, therefore, solely within the purview of the clinician. However, the identification of a specifically toxic allergen is no different in principle from the demonstration of a toxic contaminant and should be expected to include proof which fulfills the usual requirements of scientific evidence.

Some of the difficulties which attended an evaluation of the evidence concerning cottonseed allergy will serve to illustrate the complexity of the problem of dealing with discrimination which was the direct result of clinical reports of allergic disturbances attributed to foods containing cottonseed oil.

Published clinical data provide the only available criteria for determining the comparative importance of allergens as causative factors in allergic diseases. Tabulated summaries showing the frequency of reactions to specific allergens have been published by many clinicians, but the statistical value of these data is limited, owing to the fact that no standard procedure has yet been adopted for measuring the capacity of an allergic patient to react to a specific allergen. The most widely used diagnostic tests depend upon the observation of a localized response when an identified allergen is introduced by absorption through either a normal or a scratched area of the skin, or by injection of the allergen beneath the surface of the skin. A localized swelling and reddening of the skin at the site of the test comprises the positive reaction, indicating presumably some degree of specific sensitiveness to the particular allergen applied. This procedure possesses undoubted virtues, but its limitations are also worthy of recognition. An important fact is that a definite correlation has not been established between skin response to locally introduced allergens and the allergic response exhibited by other organs of the body when the same allergens are absorbed by other normal routes. A review of important published clinical data concerning cottonseed allergy will serve to illustrate some potential sources of error in the interpretation of the allergist's observations.

In a comprehensive review of clinical data and opinions concerning cottonseed allergy, Bowman and Walzer (6) cited the few published reports in which sentiveness to allergens of the cottonseed had been mentioned. They noted that A. Brown (7) and Cooke (8) had reported cottonseed sensitiveness in 2 per cent and 0.6 per cent, respectively, of their asthma cases, and that G. T. Brown (9) had found 2.4 per cent of 530 patients, including all forms of allergy, were sensitive to cottonseed. These values in the opinion of Bowman and Walzer indicated a surprisingly low incidence of identified disturbances from this seed in view of the properties and wide distribution of cottonseed products. They pointed out that the active allergen of cottonseed was considered to be a protein which was carried by the refined oil, linters or press cake, and that this allergen appeared to be of exceptionally high potency for those who manifest a sensitiveness to it. A speculative basis for the occurrence of cottonseed allergens in milk and lard from animals fed on cottonseed meal was mentioned by these authors.

Whether the data cited from the reports of A. Brown, Cooke, and G. T. Brown comprise an acceptable basis for evaluating the frequency or importance of cottonseed allergy may best be determined by examination of the original reports.

In 1923, Aaron Brown (7), under the title "Present Day Treatment of Asthma," discussed the causes, diagnosis and treatment of various forms of asthma encountered in medical practice. In emphasizing the importance of allergens as the cause of this disease, he stated that 97 per cent of his diagnosed cases of asthma were due to inhalants. He discussed the value of skin tests and indicated that their only value was in determining a potential hypersensitiveness which demanded confirmation by other means to identify the actual causative factors in asthma. A tabulated summary of 100 cases of asthma was included to illustrate the types of this disease encountered in medical practice with respect to their causative factors. Brown's classification was as follows: The 100 cases included 17 nonsensitive patients for which causative factors were not stated. The remaining 83 sensitive subjects included 39 cases of uncomplicated asthma and 44 cases in which asthma was accompanied by other respiratory diseases. The identified allergens to which the 83 sensitive patients reacted comprised a list of 13 substances, all inhalants. Evidence of sensitiveness to more than one inhalant is found in the

fact that the total number of positive reactions among 83 patients tested with 13 listed allergens was 140. Animal epithelia were the most common offenders and "dust" accounted for the greatest number of positive reactions. Among the infrequent excitants of asthma in this group was "cotton" which accounted for two of the 140 positive reactions. Brown was considering only asthma as a manifestation of allergy. He made no specific reference to cottonseed allergy and his report furnished no information about the character of the material he used to determine sensitiveness to "cotton."

The only reference to cottonseed allergy in the cited report by Cooke (8) on "New Etiologic Factors in Asthma" is found in a tabulated summary of his observations which was included to prove that dust was the most important of 24 allergens which were contributory causes in 327 cases of bronchial asthma. In these data two positive reactions to cottonseed extract provided the value of 0.6 per cent as representing the incidence of cottonseed sensitivity. Cooke was considering extrinsic causes of asthma and his report does not indicate in what form or commodity the cottonseed was presumed to be effective as a cause of this one type of allergy. Other manifestations of allergy were not considered.

The report by G. T. Brown (9) on "Cottonseed and Kapok Sensitization" was the first and most thorough study relating to cottonseed allergy. This author recognized the possible significance of the fact that products of the cottonseed are widely distributed and mentioned some of the important uses of the fiber and linters in textiles and upholstery, some items of which he demonstrated were offending factors in allergic respiratory disturbances. Other potential sources of cottonseed allergens were, in the opinion of this allergist, to be found among the products of cottonseed oil, such as soap, the edible oil and fats, including foods containing these as salad oil or shortening, and the medicated cottonseed oil and fat employed as sprays, liniments and ointments. A unique use of cottonseed oil, first mentioned in this report by Brown and since cited in several texts, was in the preparation of the beverage, gin.

The clinical data in this report are worthy of examination, since they demonstrate the somewhat speculative basis upon which identification of the source of offending allergens may depend. Brown tested the skin reactions of 530 patients suspected of having some form of allergic disease. The preparation which he used to determine sensitiveness to cottonseed, and referred to as "cottonseed protein" was a Berkefeld filtered extract of cottonseed meal, made by macerating in the cold 5 grams of cottonseed meal in 100 cc. of an aqueous solution containing 0.5 per cent NaCl, 0.275 per cent $NaHCO_3$, and 0.4 per cent phenol. Thirteen of the 530 patients showed a positive reaction to various dilutions of this extract when applied to a scratch on the skin. Among the 530 patients tested with the cottonseed extract were 214 who reacted positively also to several other allergens including foods, pollens, and animal epithelial products. Additional tabulated data and case histories concerning the thirteen cottonseed reactors provide significant information concerning the evidence of cottonseed allergy. Skin sensitiveness to cottonseed alone was exhibited by but two of the thirteen cottonseed reactors. Cottonseed was classified as the dominant allergen for six of the subjects, who showed positive responses also to one or more allergens derived from various foods, pollens and animal sources. Two foods, cat hair, horse dander, rabbit hair appeared among the most important allergens for five of the thirteen cottonseed sensitive patients. Four of this group tested with refined cottonseed oil gave negative skin tests, although one of these was sensitive to testing with a 1:1,000,000 dilution of the original extract of cottonseed meal.

Convincing evidence of clinically important allergic reactions resulting from inhalation of air-borne particles of cottonseed products and also from direct physical contact with these substances, is found in Brown's report. None of the data presented in this report, however, provide discreet evidence that the allergic disturbances considered were owing solely or in a major degree to the ingestion of edible products of the cottonseed. Nevertheless, this author submitted the conclusion that eating products derived from cottonseed or inhalation of dust from cotton can initiate allergic disturbances in those individuals who are hypersensitive to cottonseed.

In 1933, four years after G. T. Brown had published his study on cottonseed and kapok sensitization, Taub (10) reported his clinical findings which led him to emphasize the importance of cottonseed sensitiveness. Assembling the results of skin tests with about 300 allergens employed in testing 246 allergic patients, he noted that 13 individuals reacted positively to a skin test with dried extract of cottonseed. This proportion (5.3 percent) Taub compared with values derived from the publications of A. Brown (2 per cent), Cook (0.6 percent), and G. T. Brown (2.4 percent), all of which he cited as being previously reported frequencies of cottonseed sensitiveness among allergic patients.

Examination of Taub's report reveals some important misconceptions which lead inevitably to erroneous conclusions. Both A. Brown and Cooke, as noted previously, confined their considerations to only those allergic patients who exhibited symptoms of bronchial asthma. Taub's allergic group included at least three different clinical forms of allergy in addition to asthma. Taub's skin tests were done by a significantly different technic than was used by A. Brown and Cooke. Such differences make wholly unwarranted the comparison of these three sets of data. Likewise, the data of G. T. Brown and Taub are not strictly comparable owing to the fact that the former used high dilutions of saline extract of cottonseed meal and Taub used a dried extract of cottonseed. However, it is to be noted that while G. T. Brown reported 2.4 percent of 530 suspected allergic subjects sensitive to cottonseed extract, he also pointed out that 6 percent or 13 of the 216 definitely allergic patients represented the frequency of positive cottonseed reactions among allergic subjects. From this comparison it is not possible to conclude that Taub's value 5.3 percent is significantly different nor, as he stated, relatively higher than previously reported for frequency of positive reactions to cottonseed. No statement nor evidence of a positive correlation between the clinical symptoms of allergy and positive skin reactions to the cottonseed preparation used to determine cottonseed sensitiveness was included in Taub's report. The context of this report, nevertheless, implies that a large number of listed commodities derived from cottonseed, and including a few specifically named oils and plastic shortenings, are potentially important factors in allergic diseases.

Surveying the results of the published clinical studies, in which sen-

sitiveness to allergens of cottonseed is considered, demonstrates the fallacy of summarizing the separate groups of such data for statistical study or even comparison. Important differences are apparent in the methods employed by different clinicians to determine both frequency and degree of sensitiveness to cottonseed. Multiple sensitiveness further confuses the interpretation of positive evidence of sensitization toward cottonseed, except in very rare instances, when the contributory effects of separate allergens have been studied separately.

It is apparent that the major portion of available evidence concerning the role of cottonseed products in allergic diseases rests upon observations of the skin reaction to an extract of cottonseed or cottonseed press cake. To what extent the skin response can be relied upon to denote a significant degree of reactivity of other organs of the body has not yet been determined quantitatively. Admittedly useful as a guide in the diagnosis of allergic diseases the skin test is also notably unreliable. Rackemann (11), in a recent review of the current literature on allergy, pointed out two fundamental discrepancies in the skin response to allergens. First, is the fact that a positive skin test may have no clinical significance and, second, is the frequent observation of negative skin reactions to allergens that may be conclusively proved by other means to be the primary extrinsic cause of outspoken allergic symptoms. Grow and Herman (12) have recently determined that 55 per cent of a group of persons, none of whom showed detectable evidence of allergic disease, exhibited positive skin reactions to one or more substances.

Extensive inquiry has shown that a prevalent source of error in attributing allergic disturbances to ingestion of allergens rests upon incomplete evidence or erroneous assumptions with respect to the identity of a suspected allergenic component. A case in point is the previously mentioned reference to the use of cottonseed oil in preparation of gin. This unique idea, which has been restated by several authors of texts on allergy, was subjected to examination by Stevens (13), who found that among the flavoring ingredients used in this beverage were more than twenty recognized allergens, and no basis for the inference that gin might contain cottonseed allergens was discovered. Inquiry has also revealed the fact that "vegetable salad oil" and "vegetable shortening," otherwise unidentified, have on some occasions been assumed to be the cause or a contributory factor in allergic disturbances among patients who exhibited a positive skin reaction to a saline extract of fat-free residues of cottonseed or cottonseed meal.

CONCLUSIONS

Some fundamentally important concepts of allergy and the methods of identification of the extrinsic causative factors in allergic disease have been reviewed.

Clinical evidence bearing upon the occurrence of allergic disturbances attributed to allergens of the cottonseed has been assembled and examined to illustrate the fact that effective discrimination against a single class of food products may result from faulty interpretation of valid clinical data.

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CHINESE COTTON OIL*

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OUR problem of refining Chinese cotton oil is somewhat different than that confronting the majority of refiners. Where compound is the chief product, the obtaining of a bleachable or near bleachable oil is necessary. We are, however, primarily interested in salad oil, and hence, our problem was to produce an oil light enough for our purpose with one refining, if possible. It was necessary to get this color with one refining, and, needless to say, without excess loss. All the oil in question was refined through a Sharples plant, so all comparisons will be between laboratory tests and Sharples refinings.

First as to the characteristics of the oil.

Color—

The crude oil is very dark, almost black, much darker in color than the general run of domestic oil.

Odor and Flavor—Terrible—

Some of it smells as if they had thrown some of their dead brethren into the cookers. The better grades have anything but a sweet prime smell and flavor. At best, it is made from rotten and musty seed.

Moisture and Impurities—

Here they seem to have something on us. We have also noticed that this is true of English pressed oil. Peculiar as it may seem though, the English pressed corn oil is even dirtier than our domestic. The crude cotton, however, is exceptionally clean. We stored one shipment of crude Chinese oil for nearly six months, and the fatty acids in-

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