

ACUTE ALLERGIC REACTIONS INDUCED IN SUBJECTS WITH HAY FEVER AND ASTHMA BY THE INTRAVENOUS ADMINISTRATION OF ALLERGENS WITH OBSERVATIONS ON BLOOD CLOT LYSIS

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INTRODUCTION

THE constitutional reaction seen in some patients with hay fever or asthma during the course of treatment with allergenic extracts may be mainly respiratory, but in others flushing, itching, and urticaria predominate. Vascular collapse may also occur, and in some fatal reactions appears to be the cause of death. Although the effect of both subcutaneous and intravenous injections of antigens into hypersensitive experimental animals has been extensively studied, little light has thereby been thrown on allergic states in man. A better understanding of these reactions would be extremely desirable, but the conditions under which they occur in practice are rarely conducive to careful and systematic observation. A study of deliberately induced acute allergic reactions in man, therefore, seemed warranted and was accordingly undertaken.

Furthermore, the patients selected for study had presented themselves too late for conventional preseasonal treatment, and it was hoped that more rapid progress would be made if their tolerance of allergen could be quantitatively determined.

Because of the obvious hazards of such studies in man, we proceeded with great caution, choosing the intravenous rather than the subcutaneous route because we believed that a very small dose of the allergen would be sufficient to cause recognizable allergic manifestations, that they would occur promptly, that the reactions would be clear-cut, and that no reservoir of unabsorbed material would be present. Two or more physicians were present at all times, and means were at hand for immediate treatment of severe reactions.

MATERIALS AND METHODS

Five patients with allergic rhinitis (hay fever) and one patient with bronchial asthma were given intravenous injections of extracts to which they reacted by skin test and which were prepared from substances judged from the history to be a cause of symptoms. All the observations to be described were made in May, June, and July, 1954. No patients had received injections of allergens

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for ten months or more prior to these studies. One patient (Co.) had received a three-month course of injections with extracts of house dust and of alternaria four years previously, and one patient (W.) had received preseasonal treatment with injections of ragweed pollen extract for twelve years.

Some or all of the following studies were carried out on each of the six patients:

1. The skin was tested with approximately 0.02 ml. of serial tenfold dilutions of the appropriate allergen immediately before and within one hour after the intravenous injections. The highest dilution causing a clear-cut wheal and erythema was recorded.

2. Blood was drawn before and immediately after the intravenous injections to be described below in order to determine the following:

- A. Total white blood count

- B. Total eosinophil count done with eosin and methylene blue in a 5 per cent solution of acetone in water

- C. Complement titer determined spectrophotometrically¹

- D. Clotting time determined by the Lee-White method

- E. The titer of skin-sensitizing antibody (see below)

3. Oral temperatures were taken before and at the end of each experiment, and blood pressure and pulse were measured at intervals of a few minutes throughout the procedure.

4. Measurements of the vital capacity with kymographic tracings of expiration (expirogram²) were made repeatedly.

5. The patients were carefully observed, all symptoms were recorded, and the chest was examined at frequent intervals.

Skin-Sensitizing Antibody.—The titer of skin-sensitizing antibody was estimated by first determining the extent to which the serum could be diluted with normal saline solution without the loss of its capacity to sensitize normal skin (dilution technique). Serial fivefold dilutions ranging from undiluted serum to 1:625 were made. Titers were also obtained by determining the amount of allergenic extract which could be added to undiluted serum without loss of sensitizing capacity (neutralization technique). Serum was mixed with an equal quantity of a solution containing 0, 80, 300, 1,280, and 5,120 Noon units. In both procedures, 0.1 ml. was injected intracutaneously into a normal subject known to be a good recipient for passive transfer. Each site was challenged twenty-four hours later with 0.02 ml. of a solution containing 2,000 Noon units.

Procedure.—With the patients seated, intravenous injections were made into an antecubital vein from a tuberculin syringe through a No. 25 hypodermic needle. Care was taken that the injection was, indeed, given intravenously. The initial dose was 0.005 Noon units. Depending upon the degree of skin sensitivity, the dose was increased three- to tenfold at each subsequent

injection until symptoms occurred. The injections were made at intervals of ten to fifteen minutes. In two patients additional injections were given after symptoms appeared.

RESULTS

Some of the results are summarized in Table I. Four patients (W., N., I., Co.) developed clear-cut nasal symptoms which were stated by them to be identical with symptoms which had occurred spontaneously in the past.

Two reactions in W., the first reaction in N., and the reaction in Co. lasted between eight and twenty-two minutes. The second reaction in N. and the reaction in I. were promptly relieved at the end of twelve and fifty minutes, respectively, by the intravenous injection of 15 to 25 mg. of tripeleppamine hydrochloride. The second reaction in N. was accompanied by a fall in vital capacity from 5,200 to 4,200 c.c. One hour after the injection, patient Co., the only one to receive dust extract, developed nausea and chilliness, followed (from the patient's description) by a shaking chill thirty minutes later.

The fifth patient, Ca., who had not only symptoms of rhinitis but also symptoms suggestive of bronchial asthma, developed sneezing, coughing, and tightness of the chest with warmth of face and neck four and one-half minutes after the injection of 250 Noon units of ragweed extract. This was followed by abdominal pain and urgency four minutes later. Despite the cough and tightness of the chest, the vital capacity was not reduced. Twenty milligrams of tripeleppamine hydrochloride was given intravenously nineteen minutes after the onset of the reaction, followed by a decrease in the above manifestations and also by dizziness. Fourteen minutes later a brief syncopal attack occurred, with a rise in pulse but no change in blood pressure. During the entire reaction the patient appeared to be hyperventilating.

The sixth patient (H.), who had had severe asthma since childhood and had been receiving cortisone by mouth for thirteen days, was currently taking 25 mg. of cortisone four times daily. She was virtually free of respiratory symptoms. Three minutes after the injection of 75 Noon units of ragweed pollen extract (the sixth injection), the patient described dizziness followed by a "peculiar" taste in her mouth. Auscultation revealed wheezes, and the vital capacity at this time had fallen from 2,250 c.c. to 1,320 c.c. Small urticarial lesions appeared on the face but were not noted elsewhere. The patient complained of urgency and, after receiving 0.3 c.c. epinephrine 1:1,000 subcutaneously, voided. Ten minutes after the injection, the patient coughed a number of times and, upon being asked to repeat the vital capacity, fainted. The blood pressure, which had not changed in previous measurements, was 90/60 mm. of mercury at this time. She was then placed on a bed, and seventeen minutes after the injection she received 20 mg. of tripeleppamine hydrochloride intravenously. This was followed by vomiting, retching, and pain in the lower abdomen just above the symphysis pubis. Defecation occurred three times in the succeeding sixteen minutes. The patient was very restless and appeared to writhe in pain at times. She complained of a peculiar feeling radiating down her legs, which she was unable to describe, and also of pain

TABLE I. SUMMARY OF OBSERVATIONS IN SIX PATIENTS

PATIENT	AGE, SEX, AND DIAGNOSIS	DATE	ALLERGENIC EXTRACT ADMINIS- TERED	MINIMUM CONCEN- TRATION CAUSING SKIN REACTION (NOON UNITS PER MILLILITER)	DOSE CAUSING SYMPTOMS (NOON UNITS)	INTERVAL BETWEEN INJECTION AND		
						INITIAL SYMPTOMS (MINUTES)	PEAK OF SYMPTOMS (MINUTES)	END OF REACTION (MINUTES)
Co.	33 Male Urticaria and rhini- tis	6/ 2/54	House dust	2.5	250	5½	19	27
I.	26 Male Hay fever	5/27/54	Timothy	0.5	1000	10	60	60
N.	30 Male Hay fever	6/23/54	Ragweed	0.05	25 25 50	11 9 2	11 9 14	33 -- 18
W.	40 Female Hay fever	6/16/54	Ragweed	5	50 100	6 1½	7-8 5	15 9½
Ca.	20 Female Hay fever	6/30/54	Ragweed	0.05	250	4½	23	26
H.(4)	18 Female Asthma	7/ 7/54	Ragweed	0.005	75	2	11 (syncope)	52

One unit is equivalent to extract obtained from 10.⁻⁶ gram dry pollen or dry dust extract (Endo Products, Inc.).

in the lower back. At the end of forty-three minutes the patient felt more comfortable, blood was drawn, and she appeared to fall asleep. As she seemed to be well thereafter, she was sent home.

We believe it is noteworthy that skin manifestations were not prominent. One of the patients (Co.) had urticaria as his presenting symptom, but he had had rhinitis several years previously which was believed to be caused by allergy to dust; this had cleared following treatment with dust extract. A second patient (I.), whose presenting complaint was seasonal rhinitis, also had been having urticaria in the weeks immediately preceding the test. In neither of these patients was the reaction to the intravenous injections accompanied by urticaria. However, patient Co. developed some flushing and transient itching of the side of the face during the reaction.

We were surprised that changes in pulse and blood pressure were not observed in patients W., I., Co., and N. despite the appearance of clear-cut nasal symptoms, which were severe in patients I. and N. In Ca. and H., who had more severe reactions associated with fainting or near fainting directly or indirectly caused by the injection of allergenic extract, changes in blood pressure and pulse were observed, but these were not striking and were of short duration.

IVING INTRAVENOUS INJECTIONS OF ALLERGENIC EXTRACTS

DILUTION	ANTIBODY TITRATIONS		SEVERITY OF REACTION	MANIFESTATIONS	TREATMENT
	NEUTRALIZING CAPACITY (NOON UNITS PER MILLILITER)				
—	—	++		Sneezing, itching of nose, flushing of skin; shaking chill one hour later	None
:25	2000	+++		Nasal obstruction, itching of the eyes, and lacrimation	25 mg. tripeleannamine after 60 minutes
:625	320	+ ± +++		Nasal stuffiness and itching, rhinorrhea, cough, slight flushing of face	20 mg. tripeleannamine intravenously 14 minutes after the last injection
:5	80	+ ++		Sneezing, itchy throat, and rhinorrhea	None
:625	>5120	++++		Cough, "tight chest," sneezing, flushing, abdominal pain, urgency, syncope, and hyperventilation	20 mg. tripeleannamine intravenously after 23 minutes
:625	320	++++		Dizziness, urticaria, wheezing, syncope, abdominal pain, urgency, urination, and defecation	0.3 c.c. epinephrine subcutaneously after seven minutes and 25 mg. tripeleannamine intravenously after 17 minutes

For comparison with the reactions induced with allergens, patient I. was given 0.01 mg. histamine (as base) intravenously. This was followed within one minute by flushing of the face and throbbing in the head lasting more than ten minutes. There were no nasal or pulmonary manifestations, nor were there changes in the pulse and blood pressure.

Titration of skin sensitivity in Co. and I. did not show a change in end point. In Co. the erythema surrounding the test sites was markedly suppressed in the tests done after the intravenous injections. He felt well at this time but, as already mentioned, he shortly developed symptoms which culminated in a shaking chill interpreted as a pyrogenic reaction to the house dust extract.

Significant changes in the white count were not observed and, although there was a fall in the eosinophil count in four out of five instances, this was not striking. There was no change in the antibody titer as determined by either the dilution or the neutralization technique in the five patients studied in this manner. None of the six patients showed a significant change in complement titer and there was no change in clotting time in the two patients (Ca. and H.) in whom this was measured. Clot retraction was not studied quantitatively, but in one patient (Ca.) gross inspection of the clot on the following day revealed apparently normal retraction.

An unexpected finding was the absence of any visible clot (fibrinolysis) in three instances (Co., N., and H.) when blood obtained at the end of the experiment (but not that obtained before) was inspected twenty-four hours later. This was an incidental finding in the first two, but in H. it was specifically looked for. This blood specimen had exhibited a normal clotting time and the clot itself appeared to be firm and of normal consistency one hour after clotting. Though looked for in patient Ca., who had one of the more severe reactions, fibrinolysis was not observed.

DISCUSSION

The interval of two to eleven minutes between the intravenous injection and the first evidence of an allergic reaction was longer than had been anticipated. However, the procedure followed was designed to avoid giving much more than a minimally reacting dose. Although this objective was not consistently attained, nevertheless, the doses given were probably less than those ordinarily responsible for constitutional reactions arising unexpectedly during injection therapy. The small size of the dose may account for the delay in the appearance of manifestations.

With the exception of faintness, syncope, and abdominal pain in two (H. and Ca.) and a burning sensation on the face and scalp of one (H.), the symptoms produced by the intravenous injections were described by the patients as indistinguishable from those occurring spontaneously and in all but one (H.) were not described as being any more severe. In this single exception the respiratory symptoms were overshadowed by abdominal pain and incontinence, and treatment with epinephrine and then triplennamine undoubtedly modified the course of the reaction.

In spite of clear-cut respiratory symptoms and signs of an allergic reaction, significant changes in the pulse and blood pressure were not observed in four patients (Co., I., N., and W.). This and the fact that flushing of the skin was not striking in any of the patients suggest that release of histamine into the circulation either did not occur or was of insignificant degree in these reactions. Furthermore, in the patient who received histamine as well as an allergen, the former gave rise only to flushing and headache, whereas the latter produced typical hay fever.

The results obtained were in accord with the view that the nature of the manifestations produced was determined more by the location of the reactive tissue (shock tissue) than by the route of administration of the allergen.

Among the patients tested with ragweed extract, there was good correlation between the skin-sensitizing antibody titer determined by the dilution technique, skin sensitivity, and the severity of the reaction. On the other hand, there was little or no correlation between these and the dose required to produce a reaction.

The levels of skin sensitivity, circulating antibody, and complement were not influenced by doses of allergen sufficient to induce the systemic allergic reactions. The amount of antibody which, on the basis of titration done by the neutralization technique, might have been "neutralized" by the dose of allergen giving rise to a systemic reaction was contained in less than 1 ml. of the

patient's serum or perhaps 1/2,500 of that available in the circulating blood volume. Were such quantitative relationships to hold in fact, no available serologic test would be capable of detecting the changes resulting from the injection of this amount of allergen. These quantitative considerations indicate that a dose of allergen sufficient to influence significantly the titer of circulating antibody would not be tolerated by such patients. This is additional evidence that the term "desensitization" or "hyposensitization," if by this one implies appreciable diminution of circulating antibody, is misapplied to the treatment of allergic patients with injections of allergens.

The preceding quantitative considerations raise a number of questions concerning the nature of the antibody responsible for the allergic reactions induced if, as appears likely, we are dealing with conditions of extreme antibody excess. If the antibody combines with the allergen in the plasma, then either the antigen-antibody complex must be capable of inducing an allergic reaction upon reaching the tissues or dissociation of the complex must occur, permitting the allergen to attach itself to antibody fixed in the reactive tissue. Because evidence is lacking for physical combination *in vitro* between skin-sensitizing antibody, as seen in pollinosis, and the allergen, a preferable hypothesis would appear to be that no reaction between the antigen and antibody takes place in the plasma, and that only that antibody fixed in tissue can unite with the allergen. However, if antibody is fixed in reacting tissue widely dispersed in the body (skin, nose, lungs, gastrointestinal tract, and presumably elsewhere), the small amount of allergen injected in these experiments of necessity must either be very sparsely distributed or be taken up preferentially by the so-called "shock tissue." Intravenous injection presumably assured equal distribution of the allergen to all tissues in the body. Nevertheless, manifestations were chiefly in the respiratory tract. In view of the demonstrable reactivity of the skin, antibody must be present there as well as in the respiratory tract, presumably fixed to tissue. The relatively infrequent and feeble skin manifestations which followed the intravenous injections were to us a surprising finding; this is a point which is not readily explained except by the "shock tissue" concept. In order to explain the "shock tissue" concept, one may postulate one or more of the following: (1) that the tissue in the respiratory tract is more reactive than elsewhere, (2) that it takes up antigen preferentially either because it contains more antibody or because the antibody in the site is more avid, or (3) that the antibody fixed in the "shock tissue" behaved differently in some other respect from that fixed elsewhere. Localization of the "shock tissue" in the respiratory tract in these patients is presumably explained by exposure through inhalation. A means of investigating these questions is urgently needed.

Although allergic reactions were unquestionably induced in the six subjects, there was no consistent change in the white count and the downward trend in the eosinophil count can hardly be accepted as significant. This is in accord with the view that neither the leukopenic index nor a change in eosinophils is applicable for the detection of this type of allergic reaction in man.

It is of interest, perhaps, that the severest generalized reaction occurred in patient H., despite the fact that she was taking 100 mg. of cortisone daily, suf-

ficient to relieve the asthma that she had been having. As she required cortisone for recent symptoms, however, she probably had the severest allergic disease of the group studied.

So far as we are aware, fibrinolysis has not been observed hitherto in acute allergic reactions in man. Its appearance in two patients having almost exclusively upper respiratory manifestations (hay fever) suggests that such reactions in man following parenteral injections are accompanied by more widespread changes than are apparent.

SUMMARY

Six patients with allergic disease of the respiratory tract were given intravenous extracts to which they were sensitive both clinically and by skin test. Amounts which were sufficient to evoke respiratory manifestations produced little apparent circulatory or cutaneous change. No change was observed in skin sensitivity or in circulating skin-sensitizing antibody or complement. An unexpected finding was the lysis of clot formed in blood drawn after the induced reactions (fibrinolysis) in three instances.

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