ALLERGENIC RELATIONSHIP OF THE POLLENS OF DWARF AND GIANT RAGWEED TO SEVERAL OF THEIR BOTANIC RELATIVES

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The reason for studying the allergenic relationship of the pollens of the ragweeds to their botanic relatives is that information so obtained may be of value in answering certain questions of both theoretical and practical importance. These questions are: (1) Is the allergy to the pollens of these related plants a species-specific hypersensitiveness resulting from exposure to the pollen of each separate species individually or can it be explained on the basis of "crossed reactions" resulting from a primary allergy to dwarf or giant ragweed? (2) Is the (water-soluble) ragweed pollen allergen single or multiple (1)? (3) Does hypersensitiveness of the atopic type develop as the result of allergenic stimulation or as the result of some "maturation" process analogous to that believed to be involved in the formation of the human blood groups (2–4)? (4) Is the *predisposition to develop* this type of hypersensitiveness specifically directed toward certain substances in certain individuals and toward other substances in other individuals (2, 3)?

EXPERIMENTAL

Skin Tests with Serial Dilutions of Pollen Extracts

Skin tests were performed by the scratch method with serial dilutions of the following pollens: (1) cosmos (*Cosmos bipinnatus*), (2) sunflower (*Helianthus annuus*), (3) dandelion (*Taraxacum officinale*), (4) goldenrod (*Solidago altissima*), (5) dwarf ragweed (*Ambrosia artemisiaefolia*), (6) giant ragweed (*Ambrosia trifida*), (7) timothy (*Phleum pratense*), and (8) rose (*Rosa, sp.*). The extracting fluid and diluent both were 50 per cent aqueous glycerine. The tests were made on (*a*) patients with hay fever, asthma, or atopic eczema having positive skin reactions to the ragweeds in order to ascertain whether or not there is a correlation between the reactions to the ragweeds and their botanic relatives and (*b*) patients with hay fever, asthma, or atopic eczema having positive skin reactions to timothy (but not to the ragweeds) in order to determine whether this correlation (if it does exist) is specific for the ragweeds or whether it occurs also in persons having the atopic predisposition but allergic to timothy instead of the ragweeds. Rose pollen was included as a negative control, rose being a plant not botanically related to either the ragweeds or timothy.

RESULTS

Of 40 patients allergic to the ragweeds 38 gave positive tests to two or more of the four other composites. Two patients with small reactions to the ragweeds gave negative tests to the other composites. There was definite variation in the degree of reactivity to the various pollens in different patients. Some were relatively more sensitive to one pollen, others more sensitive to another. Some even gave a negative reaction to a given pollen while others

TABLE I

Case 1. Hay Fever

	Cosmos	Sunflower	Dandelion	Goldenrod	Dwarf ragweed	Giant ragweed	Timothy	Rose
1–100	+++	+++	+	+++	++++	+++	−	−
1–1,000	+	++	−	+	+++	++	−	−
1–10,000	±	+	−	±	+	±	−	−

TABLE II

Case 2. Asthma

	Cosmos	Sunflower	Dandelion	Goldenrod	Dwarf ragweed	Giant ragweed	Timothy	Rose
1–100	++++	+++	±	+++	++++	++++	−	−
1–1,000	+	+	−	±	+	+	−	−
1–10,000	−	−	−	−	−	−	−	−

TABLE III

Case 3. Hay Fever and Angioneurotic Edema

	Cosmos	Sunflower	Dandelion	Goldenrod	Dwarf ragweed	Giant ragweed	Timothy	Rose
1–100	+++	+	++++	++++	+++	+++	−	−
1–1,000	+	−	++	+++	+	±	−	−
1–10,000	−	−	−	±	−	−	−	−

gave a strongly positive reaction to the same pollen (Tables I to XII). One additional patient (of a series of 3,929 suspected allergic cases tested with dwarf and giant ragweed) gave a definitely positive test to dwarf ragweed and negative tests to giant ragweed and the four other composites. These latter tests were performed three times with the same results (Table X). Ten patients allergic to timothy but not to the ragweeds gave negative reactions also to the other composites. Table VI illustrates the results in one case.

The strong correlation between the reactions to the ragweeds and their

TABLE IV

Case 4. Hay Fever and Asthma

	Cosmos	Sunflower	Dandelion	Goldenrod	Dwarf ragweed	Giant ragweed	Timothy	Rose
1–100	++	+++	−	++	++++	+++	−	−
1–1,000	+	+++	−	±	++	++	−	−
1–10,000	−	+	−	−	+	+	−	−

TABLE V

Case 5. Asthma

	Cosmos	Sunflower	Dandelion	Goldenrod	Dwarf ragweed	Giant ragweed	Timothy	Rose
1–100	−	−	−	−	++	++	−	−
1–1,000	−	−	−	−	±	−	−	−
1–10,000	−	−	−	−	−	−	−	−

TABLE VI

Case 6. Hay Fever and Asthma

	Cosmos	Sunflower	Dandelion	Goldenrod	Dwarf ragweed	Giant ragweed	Timothy	Rose
1–100	−	−	−	−	−	−	+++	−
1–1,000	−	−	−	−	−	−	+	−
1–10,000	−	−	−	−	−	−	−	−

TABLE VII

Case 7. Asthma and Atopic Eczema

	Cosmos	Sunflower	Dandelion	Golden-rod	Dwarf ragweed	Giant ragweed	Timothy	Rose
1–100	+	++	−	++	++++	+++	−	−
1–1,000	−	+	−	+	++	++	−	−
1–10,000	−	−	−	−	++	+	−	−

TABLE VIII

Case 8. Hay Fever, Asthma, and Atopic Eczema

	Cosmos	Sunflower	Dandelion	Golden-rod	Dwarf ragweed	Giant ragweed	Timothy	Rose
1–100	+++	+++	++++	+++	+++	+++	−	−
1–1,000	++	++	++	++	++	++	−	−
1–10,000	±	−	±	±	+	+	−	−

botanic relatives is probably due to crossed reactions resulting from the reaction of antibodies with common allergenic components or with allergens of

TABLE IX

Case 9. Atopic Eczema

	Cosmos	Sunflower	Dandelion	Goldenrod	Dwarf ragweed	Giant ragweed	Timothy	Rose
1-100	++++	++++	−	+++	++++	++++	−	−
1-1,000	++	++	−	+	+	+	−	−
1-10,000	−	−	−	−	−	−	−	−

TABLE X

Case 10. Asthma, Hay Fever, and Urticaria

	Cosmos	Sunflower	Dandelion	Goldenrod	Dwarf ragweed	Giant ragweed	Timothy	Rose
1-100	−	−	−	−	++++	−	+++	−
1-1,000	−	−	−	−	++	−	+	−
1-10,000	−	−	−	−	±	−	−	−

TABLE XI

Case 11. Hay Fever

	Cosmos	Sunflower	Dandelion	Goldenrod	Dwarf ragweed	Giant ragweed	Timothy	Rose
1-100	++	+++	+	+	++++	++++	+++	−
1-1,000	+	+	−	−	+++	++	+	−
1-10,000	−	−	−	−	++	+	−	−

TABLE XII

Case 12. Hay Fever

	Cosmos	Sunflower	Dandelion	Goldenrod	Dwarf ragweed	Giant ragweed	Timothy	Rose
1-100	+++	++++	−	+++	++++	++++	−	−
1-1,000	++	+++	−	++	+++	+++	−	−
1-10,000	±	±	−	±	+	+	−	−

similar chemical composition. Another explanation, however, must be considered, namely, a species-specific hypersensitiveness to each pollen resulting from exposure to each species individually, the positive correlation being the result of a supposed individual predisposition to become sensitized to groups of allergens having a similar chemical composition. The fact that the

plants concerned are not wind-pollenated renders the possibility of exposure to these pollens unlikely and this explanation improbable. In order to obtain further information, however, the following studies were undertaken.

Antibody Neutralization

Antibody neutralization and subsequent local possive transfer were carried out by selecting six patients on the basis of their differing reactions to the

TABLE XIII

Case 3. Hay Fever and Angioneurotic Edema

Serum of patient plus extract of:	Incubated, injected into recipient, skin site tested with:							
	Cosmos	Sunflower	Dandelion	Goldenrod	Dwarf ragweed	Giant ragweed	Timothy	Rose
Cosmos	−	−	−	+	+++	+++	−	−
Rose	++	−	++	+++	+++	+++	−	−
Sunflower	++	±	++	++	+++	+++	−	−
Rose	++	±	+	++	+++	+++	−	−
Dandelion	−	−	−	−	+++	++	−	−
Rose	++	−	+++	++++	+++	+++	−	−
Goldenrod	−	−	−	−	+++	++	−	−
Rose	+	−	++	+++	++++	+++	−	−
Dwarf ragweed	−	−	−	−	−	−	−	−
Rose	+	−	+	++	+++	+++	−	−
Giant ragweed	−	−	−	−	+	−	−	−
Rose	+	−	++	+++	++++	+++	−	−
Timothy	+	−	++	+++	+++	+++	−	−
Rose	+	−	++	+++	+++	+++	−	−

ragweeds and other composites. Serum from these patients was used for *in vitro* neutralization tests (5).

The reagin-bearing serum, 0.40 cc., plus pollen extract, 1–1000 (in phenolized buffered saline solution), 0.40 cc., was drawn into a 1 cc. tuberculin syringe, thoroughly mixed, and kept in the refrigerator until the following day. This mixture was then injected intradermally into a person not allergic to any of the pollens used in subsequent tests, 0.10 cc. being injected into each of eight skin sites. These sites were marked accurately and 1 to 2 days later each was tested with a different pollen extract, 1–1000 dilution, 0.02 cc., as indicated in Tables XIII to XVIII. The controls consisted of: (1) The positive control,—the patient's reagin-bearing serum plus rose

TABLE XIV

Case 4. Hay Fever and Asthma

Serum of patient plus extract of:	Incubated, injected into recipient, skin site tested with:							
	Cosmos	Sunflower	Dandelion	Goldenrod	Dwarf ragweed	Giant ragweed	Timothy	Rose
Cosmos	−	−	−	−	+++	+++	−	−
Rose	+	++	−	++	+++	+++	−	−
Sunflower	−	−	−	±	+++	++	−	−
Rose	++	++	−	++	+++	+++	−	−
Dandelion	++	++	−	++	+++	+++	−	−
Rose	++	++	−	++	+++	+++	−	−
Goldenrod	−	−	−	−	+++	++	−	−
Rose	+	++	−	++	+++	++	−	−
Dwarf ragweed	−	−	−	−	−	−	−	−
Rose	++	++	−	+++	++++	++++	−	−
Giant ragweed	−	−	−	−	++	−	−	−
Rose	+	++	−	++	++++	+++	−	−
Timothy	+	++	−	++	+++	+++	−	−
Rose	+	++	−	++	+++	+++	−	−

TABLE XV

Case 8. Hay Fever, Asthma, and Atopic Eczema

Serum of patient plus extract of:	Incubated, injected into recipient, skin site tested with:							
	Cosmos	Sunflower	Dandelion	Goldenrod	Dwarf ragweed	Giant ragweed	Timothy	Rose
Cosmos	−	−	−	−	+	−	−	−
Rose	+++	+++	+++	+++	+++	+++	−	−
Sunflower	++	−	−	−	±	−	−	−
Rose	++++	+++	++	+++	++	+++	−	−
Dandelion	+	−	−	−	±	−	−	−
Rose	++++	+++	++	++	++	++	−	−
Goldenrod	+++	+	−	−	++	+	−	−
Rose	++++	+++	+++	++	+++	+++	−	−
Dwarf ragweed	+++	±	−	−	−	−	−	−
Rose	++++	+++	++	++	+++	+++	−	−
Giant ragweed	++	−	−	−	−	−	−	−
Rose	++++	++	+	+	++	++	−	−
Timothy	++++	++	++	+	++	++	−	−
Rose	++++	++	++	++	++	++	−	−

TABLE XVI

Case 9. Atopic Eczema

Serum of patient plus extract of:	Incubated, injected into recipient, skin site tested with:							
	Cosmos	Sunflower	Dandelion	Goldenrod	Dwarf ragweed	Giant ragweed	Timothy	Rose
Cosmos	−	+	−	+	+++	+++	−	−
Rose	++	++	−	+	+++	+++	−	−
Sunflower	−	−	−	−	+++	+++	−	−
Rose	++	++	−	+	++++	+++	−	−
Dandelion	++	++	−	++	++++	++++	−	−
Rose	++	+++	−	++	++++	++++	−	−
Goldenrod	+	++	−	−	+++	+++	−	−
Rose	+	++	−	+	+++	+++	−	−
Dwarf ragweed	−	−	−	−	−	−	−	−
Rose	++	++	−	++	++++	++++	−	−
Giant ragweed	−	−	−	−	−	−	−	−
Rose	+	+	−	++	+++	+++	−	−
Timothy	++	++	−	++	++++	++++	−	−
Rose	++	++	−	++	++++	++++	−	−

TABLE XVII

Case 11. Hay Fever

Serum of patient plus extract of:	Incubated, injected into recipient, skin site tested with:							
	Cosmos	Sunflower	Dandelion	Goldenrod	Dwarf ragweed	Giant ragweed	Timothy	Rose
Cosmos	−	−	−	±	+++	++	+++	−
Rose	+	+	−	+	++++	+++	+++	−
Sunflower	+	−	−	±	++++	+++	++++	−
Rose	++	++	±	++	++++	++++	++++	−
Dandelion	+	+	−	+	++++	++++	+++	−
Rose	+	+	−	+	++++	++++	+++	−
Goldenrod	−	−	−	−	++++	++++	++++	−
Rose	++	++	−	++	++++	++++	++++	−
Dwarf ragweed	−	−	−	−	−	−	+++	−
Rose	+	+	−	+	+++	+++	+++	−
Giant ragweed	−	−	−	−	++	−	+++	−
Rose	+	+	−	+	+++	+++	+++	−
Timothy	±	+	−	+	+++	++	−	−
Rose	+	+	−	+	+++	+++	+++	−

pollen extract injected into skin sites which were subsequently tested with the various pollen extracts. (2) The negative control,—the various pollen extracts injected into previously unprepared (normal) skin sites. (3) The specificity control,—rose pollen extract injected into a previously prepared skin site. Only one serum-pollen mixture was injected into a given recipient at one time in order to avoid the possibility of one pollen extract diffusing from its injection site and neutralizing reagins at some other injection site, that is to say reagins which had previously been mixed with some other pollen extract. New all-glass tuberculin syringes were used, a separate syringe being

TABLE XVIII

Case 12. Hay Fever

Serum of patient plus extract of:	Incubated, injected into recipient, skin site tested with:							
	Cosmos	Sunflower	Dandelion	Goldenrod	Dwarf ragweed	Giant ragweed	Timothy	Rose
Cosmos	−	−	−	+	+++	+	−	−
Rose	++	++	−	+++	++++	+++	−	−
Sunflower	−	−	−	−	+++	++	−	−
Rose	+++	++	−	+++	++++	+++	−	−
Dandelion	++	++	−	++	+++	+++	−	−
Rose	++	++	−	++	++++	+++	−	−
Goldenrod	−	±	−	−	++	+	−	−
Rose	++	++	−	++	+++	+++	−	−
Dwarf ragweed	−	−	−	−	−	−	−	−
Rose	++	++	−	++	+++	++	−	−
Giant ragweed	±	±	−	+	+	−	−	−
Rose	++	++	−	+++	++++	+++	−	−
Timothy	−	−	−	−	−	−	−	−
Rose	−	−	−	−	−	−	−	−

assigned to each test pollen extract and another to each neutralizing pollen extract. It was not used for any other allergen.

RESULTS

1. In five cases dwarf ragweed completely neutralized reagins for itself and all other composites tested, indicating that, in these cases, dwarf ragweed could have been the only sensitizing allergen, *i.e.* the substance to which the patients were exposed and which stimulated the production of hypersensitiveness to itself and to the other composites (Tables XIII, XIV, XVI to XVIII).

2. In one case giant ragweed (and also dwarf ragweed) completely neutralized

reagins for itself and for all other composites tested, indicating that, in this case, giant ragweed could have been the only sensitizing allergen (Table XVI).

3. In one case no single pollen completely neutralized reagins for all other pollens although cosmos completely neutralized reagins for itself and all other composites tested except dwarf ragweed, and the latter, and also giant ragweed completely neutralized reagins for themselves and all other composites tested except cosmos. In this case none of the pollens used in these tests could have been the only sensitizing allergen although this allergen may have been the pollen of some other composite or it may have been a combination of cosmos and either or both of the ragweeds (Table XV).

4. In four cases giant ragweed, while completely neutralizing reagins for itself and for the other composites, failed to neutralize completely reagins for dwarf ragweed, thus proving that, in these cases, giant ragweed could not have been the only sensitizing allergen because the patient's serum contained reagins for an allergen (or allergens) not present in giant ragweed.

5. Cosmos, sunflower, dandelion, and goldenrod, while capable of completely neutralizing reagins for themselves and frequently for one another, failed to neutralize completely reagins for dwarf ragweed and also (with one exception, case 8, Table XV) for giant ragweed, thus proving that, in none of the 6 cases studied could these pollens have been the only sensitizing allergens because the patient's serum contained reagins for an allergen (or allergens) not present in these pollens.

DISCUSSION

In the geographical area in which these patients live the pollen of dwarf and giant ragweed (especially the former) is known to be present in the atmosphere in high concentration in August and September, as demonstrated by pollen counts (6), whereas the pollen of the four other composites is never (or rarely) found on slides exposed for pollen counts. Hence the pollen to which these patients are known to have had repeated exposure is the same as that which, by immunologic study, has been shown to contain allergens for all the reagins present in the patient's serum and therefore the pollen which could have been the only sensitizing allergen. The pollens of the four other composites, to which these patients have probably not been exposed (except possibly case 8 to cosmos), are those which immunologic study has shown to be incapable of having produced the hypersensitiveness. These facts constitute evidence in support of the proposition (widely accepted and supported by other evidence) that hypersensitiveness of this type develops as the result of allergenic stimulation rather than in some other manner.

The varying reactions of different patients to the pollens of the non-wind-pollenated composites, even though they were probably sensitized as the result of exposure to the same pollen (*e.g.* cases 3 and 4, Tables III, IV, XIII, and

XIV), indicate that two patients, exposed to the same pollen, may develop hypersensitiveness having qualitative differences. Their reagins also may differ qualitatively. These facts may best be explained by supposing that the pollen of each species contains, in addition to its species-specific allergen or allergens, at least several common determinants which vary in their distribution among various related species. Thus one patient, exposed to the pollen of a given species containing multiple allergenic groupings, may become sensitized to certain groupings but not to others, while another patient, exposed to the same pollen, may become sensitized to a different group of the components.

SUMMARY

Thirty-eight of forty patients, allergic to the pollen of dwarf and giant ragweed, were found to be allergic also to the pollen of botanically related species. There was definite variation in the degree of reactivity to the various pollens in different patients. One additional patient reacted to dwarf ragweed but not to giant ragweed or to four other composites.

Antibody neutralization studies in six cases indicated that (*a*) in four cases dwarf ragweed could have been the only sensitizing allergen. (*b*) In one case either dwarf or giant ragweed could have been the only sensitizing allergen. (*c*) In one case cosmos plus either of the ragweeds or some undetermined pollen could have been the sensitizing allergen. (*d*) In none of the six cases studied could cosmos, sunflower, goldenrod, or dandelion have been the only sensitizing allergens.

The evidence presented supports the following concepts: (1) Hypersensitiveness of this type develops as the result of allergenic stimulation. (2) The pollens of the ragweeds and their botanic relatives contain, in addition to species-specific allergens, multiple common allergenic determinants which vary in their distribution among related species. (3) A person exposed simultaneously to a group of allergens may become sensitized to certain members of the group and not to others, while another person, exposed to the same group of allergens, may become sensitized to different members of the group.

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