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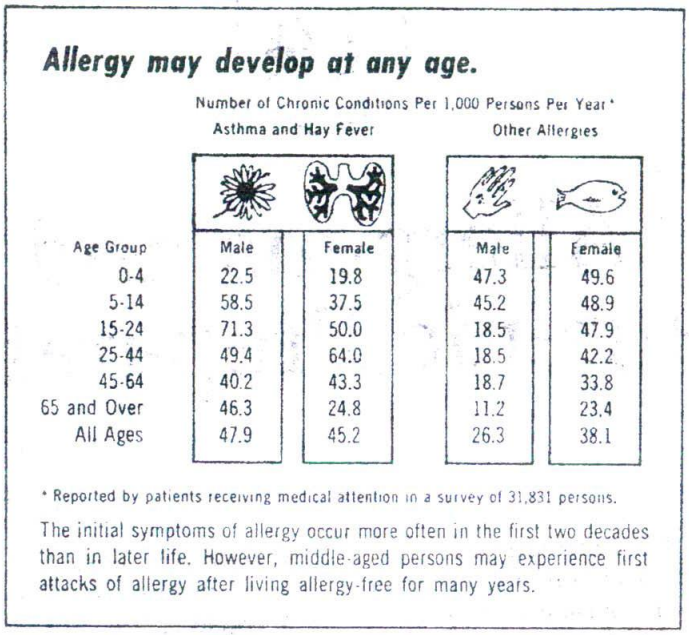
Allergens and Allergenic Preparations

Allergy has been a medical specialty for more than 50 years, although symptoms of allergic diseases have been recognized for centuries. Probably the first reference to allergic diseases was found in the Papyrus Ebers, in which asthma and diseases caused by "autointoxication" were mentioned. The writings of Hippocrates record at least 12 instances of asthma; the first case of hayfever symptoms was recorded by Herodotus. The term **allergy** was first defined in 1906 by von Pirquet in describing a changed or altered reaction in the body. When an individual develops an unusual response to a substance or condition that is harmless to others, the individual is said to be **allergic.** According to published figures, approximately half the population of the United States suffers from some sort of allergic syndrome; however, it is estimated that only one person in 10 develops symptoms sufficiently severe to require the services of an allergist or a physician who specializes in allergic diseases (Fig. 14–1).

The exact cause of allergy is still undetermined, and much investigative research is devoted to this fascinating subject. The reasons why certain individuals exhibit an allergic response to ragweed pollen and others do not are not understood. Based on genetic studies, medical and immunologic investigators generally agree that the tendency to be allergic is hereditary (Fig. 14–2). However, at the present time, it is impossible to predict whether a newborn infant will be allergic or not. Perhaps future research into the pathophysiology of allergy will reveal the answers.

Allergens are antigenic substances capable of sensitizing the body in such a way that unusual responses occur in hypersensitive individuals. Almost any substance, whether of biologic, chemical, or synthetic origin, may prove to be **allergenic.** In addition, numerous other factors are allergy-producing, such as emotional factors, atmospheric factors, psychosomatic factors, and chronic types of infection. However, because most allergens are composed of plant or animal matter, they merit consideration in a treatise on natural products.

The allergen concerned with the patient's symptoms must be **antigenic;** that is, it must be capable of eliciting an antibody response. The antigenic fraction of ragweed pollen, for example, causes a susceptible person's body to produce special protein molecules **(antibodies),** some of which circulate in the blood **(circulating** antibodies) and others of which become attached to the cells of the nasal membranes (**fixed** antibodies). These particular antibodies have a special affinity for the chemical components of ragweed pollen and of



Allergy may develop at any age.

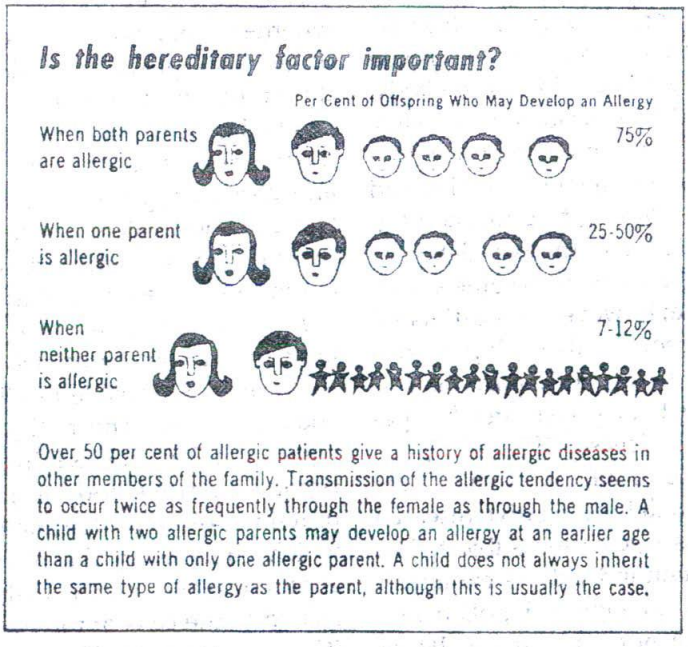
Number of Chronic Conditions Per 1,000 Persons Per Year *

Age Group	Asthma and Hay Fever		Other Allergies	
	Male	Female	Male	Female
0-4	22.5	19.8	47.3	49.6
5-14	58.5	37.5	45.2	48.9
15-24	71.3	50.0	18.5	47.9
25-44	49.4	64.0	18.5	42.2
45-64	40.2	43.3	18.7	33.8
65 and Over	46.3	24.8	11.2	23.4
All Ages	47.9	45.2	26.3	38.1

* Reported by patients receiving medical attention in a survey of 31,831 persons.

The initial symptoms of allergy occur more often in the first two decades than in later life. However, middle-aged persons may experience first attacks of allergy after living allergy-free for many years.

Fig. 14–1. Chart showing comparison of incidence of allergic response in males and females. (Courtesy of Burroughs Wellcome & Co., Inc.)



Is the hereditary factor important?

Per Cent of Offspring Who May Develop an Allergy

When both parents are allergic — 75%

When one parent is allergic — 25-50%

When neither parent is allergic — 7-12%

Over 50 per cent of allergic patients give a history of allergic diseases in other members of the family. Transmission of the allergic tendency seems to occur twice as frequently through the female as through the male. A child with two allergic parents may develop an allergy at an earlier age than a child with only one allergic parent. A child does not always inherit the same type of allergy as the parent, although this is usually the case.

Fig. 14–2. Chart showing probability figures for inheriting a tendency toward allergy. (Courtesy of Burroughs Wellcome & Co., Inc.)

related pollens in the ragweed family, but they cannot combine with the antigenic molecules in unrelated pollens, in foods, or in other allergenic substances. Thus, antibodies are considered **specific,** and, because allergenic substances do produce specific antibodies, each type of allergy is constitutionally different from other types.

When the body is first subjected to the allergen (antigen), the condition is referred to as the **primary exposure.** Because no antibodies have been formed previously, no symptoms of the allergy are produced during the primary exposure. However, during the subsequent exposures, the allergen contacts the fixed antibodies and an **antigen-antibody reaction** occurs.

Predisposing factors that may make some persons susceptible to allergy are (1) hereditary tendency to allergic response, (2) dysfunction of the endocrine glands, (3) increased excitability of sympathetic and parasympathetic nervous systems, (4) absorption of toxic metabolic and catabolic substances, (5) hepatic dysfunction, and (6) psychic influences.

The antigen-antibody reaction causes a liberation of **histamine** and other mediators of allergic symptoms, including **leukotriene C** or **SRS** (slow-reacting substance) and **bradykinin** (from the cells of certain tissues and organs referred to as the **shock tissues** or **shock organs).** If the state of shock is confined to the area of the introduction of the allergen, the condition is a localized reaction; if its effects extend beyond this area, it may be a generalized or constitutional reaction. The constitutional reactions produced in some patients by injections of penicillin preparations are extremely uncomfortable and sometimes dangerous—even fatal.

The types of symptoms depend on the shock organ affected by the particular allergen and its path of entry into the body. Substances that are distributed in the atmosphere and contact the nasal or buccal mucosa during respiration are **inhalant** allergens; those that occur in foodstuffs and are swallowed are **ingestants;** those that may be present in solutions intended for parenteral administration are **injectants;** and those that come into direct contact with the epithelium are **contactants.**

Still other types are represented by the metabolic wastes and growth products of pathogenic microorganisms **(infectants)** and of parasitic microorganisms in or on the body **(infestants).** In addition to these material allergens, allergies may be caused by heat or cold (physical allergy), changes in climate (environmental allergy), anger or frustration (psychosomatic allergy), and others.

In an attempt to discover the causative factors of a patient's symptoms, the allergist records a complete case history, including a review of possible allergies shown by other members of the patient's family. The type of symptoms, whether gastrointestinal, bronchial, or epidermal, whether localized or general, whether seasonal or perennial, afford a starting point for the allergist's diagnosis.

INHALANT ALLERGENS

If the symptoms are restricted to the nasal mucosa and are manifested by sneezing, lacrimation, itching, and swelling of nose and eyes, an inhalant allergen is usually indicated. (However, certain food allergens also cause such symptoms.) The condition is known as **sinusitis** or **hayfever.** The term "hayfever" was originated by John Bostock in England over a century ago because he believed that the odor emanating from new-mown hay was responsible for the "fever" or stuffiness of the nasal passages. Occurrence of the symptoms during certain months of the year indicates **seasonal** hayfever. Because this condition is usually associated with the release of pollen grains from certain plants, the term **pollinosis** is often used. **Nonseasonal** hayfever, more commonly called **perennial rhinitis,** may be caused by inhalants other than pollens: mold spores,

dust, animal epidermis or dander, feathers, cotton linters, volatile oils, and countless other factors.

In the case of seasonal hayfever, determination of the exact dates within which symptoms occur frequently gives a clue to the type of pollen grains responsible for the allergy. In all but the extreme southern and southwestern states, 3 well-defined pollen seasons exist: (1) the tree season in spring, extending from February until June; (2) the grass season in late spring and early summer, principally from April until August; and (3) the ragweed season in late summer and early fall, beginning the first week in August and continuing until mid-October. Variations in the pollinating periods of these plants are directly related to geographic locations, severity of winters, and similar factors. Published sources are available that divide the United States into different regions. Additional authentic information is distributed by the American College of Allergists, the American Academy of Allergy, and the Allergy Foundation of America.

Because of their heterogeneous nature, pollen grains can be distinguished and identified without difficulty. Pollen grains may be round, oval, angular, square, rectangular, or otherwise shaped, depending on whether they are contracted or fully expanded. Most pollen grains are single entities, but some may be 2-compound, 3-compound, tetrads, and so forth. They may have no **germinal apertures** as such (acolpate), have many pores (multicolpate), or range in-between (dicolpate, tricolpate, tetracolpate). The outer wall is known as the **exine** and the inner wall as the **intine.** The surface appearance of the exine is characteristic and is a determining factor in identification; it may range from smooth (psilate) to spiny (echinate), with various intervening gradations (reticulate, granulate, lophate).

Atmospheric pollens are liberated chiefly by **anemophilous** (wind-pollinated) plants and are usually small (15 to 45 μ in diameter), light, nonadhesive, and relatively smooth (Fig. 14–3). Trees (oak, walnut), grasses (Bermuda grass and timothy), and weeds (ragweed, plantain) are examples of plants having anemophilous flowers. In contrast, pollens of **entomophilous** (insect-pollinated) plants are usually larger (up to 200 μ in diameter), heavier, adhesive, and may be somewhat spiny. Plants with scented, colored flowers (clover, hollyhock, honeysuckle, rose) are entomophilous. Wind-pollinated flowers are rarely colored and are generally not fragrant because they do not need to attract insects for the pollination process.

Nonseasonal hayfever, as the name indicates, cannot be related to a seasonal trend. The allergic symptoms may be manifested throughout the entire year or perhaps at several periods during the year but with no regularity. Often inhalant allergens may occur in the home, at the place of employment, or in some particular locale frequented by the patient. In the home, cotton pillowcases, sheets, and blankets usually shed "linters" or fragments of cotton fibers that are light enough to float in the air. The pillows, if made of feathers, may be a source of the allergen, particularly if the pillows are old and the feathers are disintegrating. If a person has a sensitivity to feathers, he should use a foam rubber pillow or should cover the feather pillow with a plastic, dust-free cover. Sometimes a pet canary or parakeet may cause a feather sensitivity.

Odors and perfumes are a major factor in nonseasonal allergy. The increased desire for unusual scents in toiletries and cosmetics has led manufacturers to use volatile oils from many new plant sources as ingredients in their formulations. For example, sandalwood oil is an ingredient in some men's toiletries; however, photoallergy to sandalwood oil has been reported in the medical literature. Many other volatile oils are allergenic. Removal of the allergens by substituting nonscented cosmetics brings relief (see page 423).

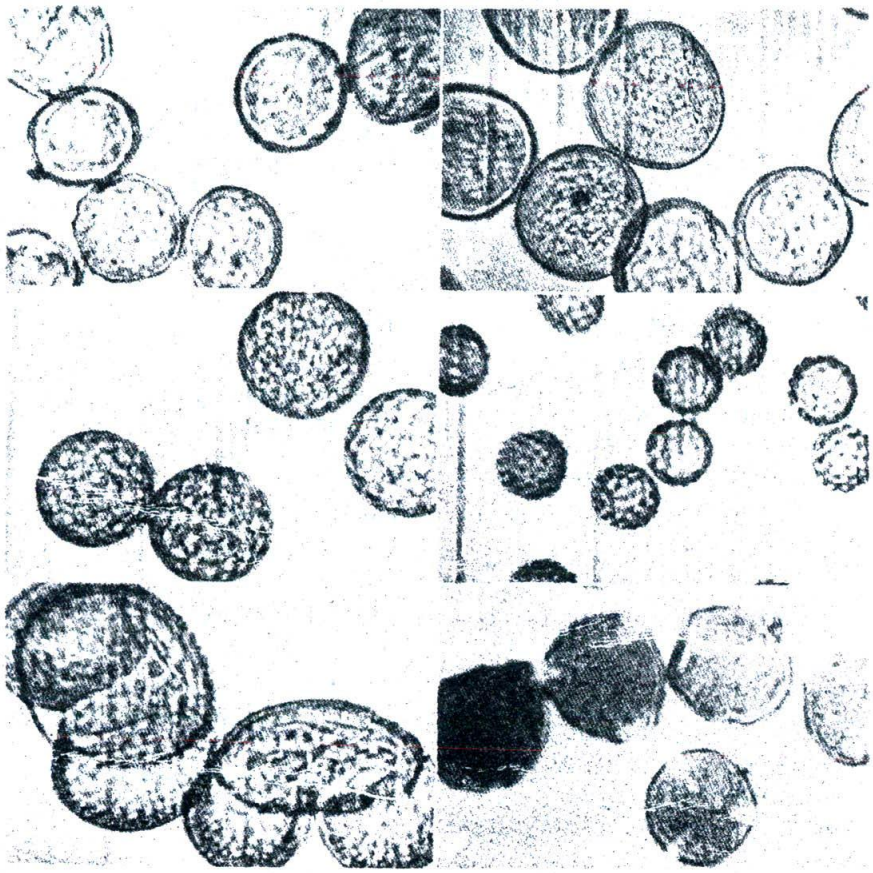


Fig. 14–3. Photomicrographs of pollen grains. *A*, American elm; *B*, orchard grass; *C*, lamb's quarters; *D*, giant ragweed; *E*, pine; *F*, white oak. All magnified to same scale: each space on the micrometer scale equals 3.2 microns.

Animal epidermis or **animal dander** (epithelial scales) is a frequent source of allergenic matter. Cats, dogs, guinea pigs, and other pets are occasionally responsible for a patient's cough, wheeze, or asthmatic attack. Treatment with dander extracts does not always result in a significant number of improved cases, and the therapy of choice is avoidance of exposure. Sometimes patients are affected by the odors of the animals rather than by the dander. Any type of furniture stuffed with horsehair or other animal material should also be investigated as a cause of nonseasonal hayfever.

The allergen present in castor beans is often the cause of severe allergic reactions. The allergen is not removed with the oil when the seeds are expressed, but it does cause difficulty in the processing plant. Because this allergen is air-borne and windborne, persons living in the vicinity of industrial factories that make or use castor bean pomace may exhibit allergic reactions.

Much of the nonseasonal hayfever is thought to be caused by fungus spores, especially of such molds as *Alternaria* (see Fig. 14–10), *Helminthosporium*, *Hormodendrum (Cladosporium)*, and *Aspergillus*. Mold spores are almost constantly present in the atmosphere, even during winter, and have been traced as the contributing factors to many cases of perennial rhinitis. *Aspergillus*, *Penicillium*, and other molds abound in moist places and occur in cellars and in damp cupboards.

Persons allergic to mold spores are usu-

ally allergic to dust as well. Dust is almost indefinable because it differs from one place to the next, but it probably is composed of mold spores, cotton linters, animal danders, sizing from rugs and carpets, and innumerable other allergenic particles. Various types of mites have also proved to be major allergens in house dust, particularly the acarine mite, *Dermatophagoides*, and specifically its species, *D. pteronyssinus*.

Several years ago, the Allergy Research Laboratory of Northwestern University reported that nearly 30% of patients with symptoms of asthma or hayfever are sensitive to disintegrating bits of insect dust inhaled from air and soil; thus, a clinical diagnosis of "sensitivity to dust" is inadequate.

INGESTANT ALLERGENS

Food allergens ordinarily cause gastrointestinal symptoms, but they may also cause skin rash, puffed lips and tongue, migraine, rhinitis, or other more serious effects, such as bronchial asthma. Severe cases of eczema of the hands have been caused by allergenic foods. In food allergy, the activity of the allergen is not localized in one organ or area of the body but is transferred to other organs by the blood. Thus, an **atopic dermatitis,** such as a tomato rash, strawberry rash, or that caused by eating oranges, chocolate, or shellfish, is developed by the patient. No doubt, many persons who exclaim "Cucumbers don't agree with me!" have discovered the hard way (trial and error) that they have an allergy to certain foods. Such persons may not know that they have an allergy, but they do know that eating certain foods leads to dire consequences.

Some of the most common allergens ingested by children are foods considered essential to proper diet and growth, such as cow's milk, orange juice, cod liver oil, or other vitamin-containing fish liver oils. Colic may sometimes be an allergic manifestation to a food substance, just as dermatitis may indicate a hypersensitivity to other foods. Hundreds of extracts of foodstuffs are commercially available as single or multiple units for use by the allergist as diagnostic skin test materials; however, they have little or no value in therapy. The most satisfactory method of combating food allergies is elimination of the offending substance from the diet.

Milk allergy is a specific immunologic, antigen-antibody response caused partially by a lactalbumin. Because heating or boiling alters this protein, evaporated milk may be used as an effective substitute for cow's milk. Milk allergy may result in severe dermatitis, recurrent rhinorrhea, bronchitis, and asthma. Various commercial milk substitutes that are prepared from soybean isolates offer a milk-free formula claimed to be devoid of antigenicity. Two of these soybean products are Soyalac® and Prosobee®.

It has been definitely determined that coffee can produce an allergic response. The principal water-extractable allergenic component of green coffee is chlorogenic acid (3-caffeoylquinic acid). Some authorities disagree about the allergenic properties of chlorogenic acid, claiming that the coffee-roasting process alters its structure. Various symptoms of coffee allergy have been reported: severe migraine, gastroenteritis, and widespread hives.

INJECTANT ALLERGENS

Allergic reactions to penicillin injections are well-known to most of the lay public. More attention has been called to the allergies following penicillin injections than has been given to all other allergies produced by the injection method. It is estimated that anaphylactic reactions to penicillin occur with a frequency of 1 to 5 per 10,000 patient-courses of penicillin. Once a patient has suffered a penicillin reaction, he is keenly concerned about the next injection he may receive. Skin testing for

penicillin allergy is of definite value, but tests must be conducted under controlled conditions.

6-Aminopenicillanic acid (6-APA) and 7-aminocephalosporanic acid (7-ACA), as well as the semisynthetic penicillins and cephalosporins, cause positive intracutaneous reactions in most susceptible patients. For this reason, antibiotics such as the cephalosporins and semisynthetic penicillins should be used with caution by physicians treating patients who are sensitive to penicillin G.

In addition to penicillin products, other injectables may cause allergies—liver extract, antitoxins, and the glandular products. The symptoms in each case are similar to those caused by the antibiotic: itching of the palms of the hands and the soles of the feet, erythema, and peeling of the skin are characteristic.

Because bees, hornets, and wasps actually "sting" instead of "bite," such insects are considered a source of injectant allergens. Stings of such insects can induce severe local and constitutional reactions, sometimes causing death. In fact, it has been estimated that more people die annually from bee stings and wasp stings than from snakebites. Such patients can be immunized by using injections of antigens because one antigen is common to all bees and wasps (see page 426), however, each species has its own additional distinct antigen(s).

Considerable research is being conducted on this subject at the present time. Immunologic comparisons of the effects of insect venoms, venom sac extracts, and whole insect extracts have been made to determine the optimal method of treatment. Not only are the hymenopterous insects being studied, but many of the "biting" arthropods are the subjects of clinical investigations. Among these forms are spiders, mites, lice, chiggers, ticks, sand flies, stable flies, horse flies, scorpions, centipedes, and numerous others indigenous to the geographic area of the investigators.

CONTACTANT ALLERGENS

Many substances and products have been recognized as the cause of contact allergies. One of the most important of these is the well-known poison ivy, *Toxicodendron radicans* (L.) Kuntze. Other allergenic species of the genus *Toxicodendron* (formerly *Rhus*) include *T. diversilobum* (T. & G.) Greene (known as western poison oak), *T. quercifolium* (Michx.) Greene (known as eastern poison oak), and *T. vernix* (L.) Kuntze (known as poison sumac, poison elder, or poison dogwood). All of these contain the same nonvolatile, phenolic principle, **urushiol**, and all produce allergic symptoms in hypersensitive individuals. Watery blisters associated with pruritus are indicative of this affliction which can become quite distressing if not properly treated. The blisters break open, and the exuding fluid forms new blisters that spread quite rapidly.

Other plant excitants of contact dermatitis are asparagus, buckwheat, buttercups, catalpa leaves, chrysanthemums, daffodils, English ivy, ginkgo leaves, lobelia, marigolds, mayapple, osage orange, flowering spurge, snow-on-the-mountain, smartweeds, and dozens of others. Occasional contact dermatitis has been caused by **aeroallergens**, such as the various pollen grains that contain oils, hairs from different kinds of leaves and flowers, and even small fragments of plant tissue carried by smoke emanating from brush fires, grass fires, and burning leaves.

A number of cosmetic manufacturing companies have removed certain known irritants and allergens from their beauty products and consequently use the term **hypoallergenic cosmetics** to denote this fact. Products bearing the brand names of Ar-Ex, Allercreme, Almay, and Marcelle are examples of hypoallergenic cosmetics. Orris root, an ingredient in "violet" talcum powders, is a chief contact allergen. Dibromofluorescein, commonly used in indelible lipsticks, is another. Because per-

fumes can be allergenic, many hypoallergenic products are unscented; in others, the perfuming agents are carefully screened to eliminate possible allergens.

Frequently, individuals cannot tolerate wool in clothing, blankets, or even in the form of wool fat (lanolin) in cosmetics. Soaps and soap powders, plain and enzyme detergents, nail polishes and nail polish removers, and hair dyes and hair sprays are listed among the numerous major causes of contact dermatitis.

INFECTANT ALLERGENS

Numerous living organisms may cause allergy through the products they release during their metabolism in the human body. Some individuals harbor certain types of bacteria, protozoans, molds, helminths, and other parasitic forms which, by their continual presence in the body, are responsible for chronic illness. The patient may or may not be aware of this infection because it may or may not manifest recognizable symptoms. Metabolic products of growth of these organisms may be of such nature that the individual becomes sensitized.

The chronic bacterial infection of the bronchioles, known as bronchiectasis, in which the constant presence of bacterial wastes may sensitize the allergic individual, is an example. Thus, the person may exhibit allergic symptoms but does not respond positively to skin tests for inhalant allergens. In this case, the bacterial metabolic wastes are considered infectant allergens.

INFESTANT ALLERGENS

In a manner somewhat similar to the infectants, parasitic organisms may sensitize the human body. Invasions of hookworms, tapeworms, pinworms, threadworms, dermatophytes, and other forms have caused allergic responses in susceptible individuals. Growth products and metabolic wastes of these parasites are constantly present in the body and are referred to as infestant allergens.

CASE HISTORY

To determine the circumstances surrounding the patient's allergy, the allergist must record all details regarding the allergic attacks, including data on the type of occupation and the familial background. Information concerning the place, time, and mode of onset of past symptoms, as well as those causing the most recent attack, is recorded in the case history or allergic history of the individual. As stated on a typical case history report, the entries include:

- name and sex
- marital status
- occupation
- chief complaint
- present illness
  - age of onset
  - date of first attack
  - place, time, and mode of onset
  - seasonal variation
  - duration
  - what relieves attacks
- present attack
  - date of onset
  - place of onset
  - mode of onset
  - sneezing
  - nasal discharge
  - wheeze
  - cough
  - headache
- symptoms affected by
  - meals
  - drugs
  - exertion
  - excitement
  - weather changes
  - wind
  - smoke or fumes
  - time of day
  - mowing lawn

rain
working in garden
automobile rides
playing golf
riding horse
feeding stock
cleaning house
change of season
change of environment
change of occupation

Other points of information include the types of medication the patient may be taking and the conditions of the home environment (heating system, type of floor covering, presence of household pets, kinds of cosmetics used, nature of bed covers and pillows, and numerous other details). A past medical history may be requested. Allergic symptoms of the paternal and maternal relatives are frequently a clue.

A complete case history includes both a physical and a laboratory examination, the latter to include reports on urine, blood, sputum, and nasal smears. In addition, results of a radiograph and an electrocardiogram are customary. Following or concurrent with the laboratory examination, the allergist makes his diagnosis and attempts to confirm it by the use of skin tests.

SKIN TESTS

Skin tests are conducted in 2 principal ways: (1) by **scratch tests** administered similar to the way a smallpox vaccination is administered, i.e., scratching the skin and introducing an extract of the allergenic substance; or (2) by **intradermal (intracutaneous) tests** in which a small quantity of the extract is injected between the layers of the skin.

Allergenic extracts are stable preparations of various antigenic substances and are used for diagnosis, preseasonal prophylaxis, and treatment of allergies (except food allergies).

In each case, the allergenic extract represents a solution of the chief constituents of the tested material. (Preparation of extracts involves the use of one of several standard extracting fluids: Coca's fluid, normal saline solution, purified water, dilute glycero-dextrose solution, and others.) By injecting a small amount, usually 0.1 ml, into the arm of the patient, the allergist can observe the resulting reaction within 20 minutes and classify it using the scheme shown in Table 14–1.

A skin test, then, is actually a localized reaction that determines whether the patient responds to that particular allergen. Although not infallible, skin tests are quite useful in determining sensitivity to inhalants, injectants, contactants, and some ingestants, although the reactions with the ingestants are less reliable than those with the other allergens.

Ordinarily, contactants are applied as a **patch test,** in which the material is applied directly to the skin, which is neither scratched nor penetrated with a needle. As a general rule, patch tests require a much longer time for the reaction to occur—at least 48 hours but sometimes 4 to 5 days. The offending allergen need not be extracted for applications to the skin in this type of test.

Other tests, such as the ophthalmic test, passive transfer (Prausnitz-Küstner) test, and microscopic examination of nasal secretions, may be employed by the physician as occasion demands.

TREATMENT

If the patient has a case history of allergy and exhibits a positive reaction to ragweed pollen extract, the allergist will probably resort to the **hyposensitization** method of treatment. At regular intervals, a measured amount of the greatly diluted extract is injected subcutaneously. The dose is gradually increased until the patient can withstand the inhalation of the normal seasonal atmospheric concentration of ragweed pollens with little ill effect. Complete freedom from symptoms is rarely accomplished be-

Table 14–1. Clinical Designations of Skin Reactions

Designation	Symbol	Characteristics
Negative	–	No reaction or no different than control
Doubtful	±	No appreciable difference from control other than slight erythema
One-plus	+	Erythema smaller than 20 mm in diameter
Two-plus	+ +	Erythema larger than 20 mm but no wheal
Three-plus	+ + +	Definite wheal with surrounding erythema
Four-plus	+ + + +	Wheal with definite pseudopods and erythema

cause of the inadequacy of the extracting fluids; in addition, because the identity of the allergenic fraction has not been definitely established chemically, it cannot be assayed in the completed extract.

Pollen extracts are made on a weight-volume basis using defatted pollen and are standardized according to the number of pollen units, protein nitrogen units, or total nitrogen units, depending on the laboratory policy. One pollen unit (called a **Noon unit**) represents the activity in 0.001 mg of pollen. The strength of protein extracts is expressed in terms of mg of protein nitrogen per ml; however, some laboratory workers utilize the number of mg of total nitrogen per ml, and others refer to the weight-volume formula used in extracting the allergen. At the present time, no standard is generally recognized although measurement of protein nitrogen is perhaps the most accepted method.

Most of the research on pollens has been concentrated on those of ragweed. More is known about ragweed pollens than about any others, but a great deal must still be learned. Although highly active materials have been extracted from ragweed pollens, the identity and properties of these substances have not been positively determined. By using gel diffusion methods, 6 to 8 different antigens have been demonstrated in ragweed pollens, but it is not definitely known which of these are of greatest significance in human allergy.

Numerous investigators are studying the allergenic fractions of ragweed and other pollens. Much of this research involves the use of more selective extracting fluids, the preparation of alum-precipitated and ammonium sulfate-treated extracts, the application of chromatographic and electrophoretic means of analysis, and a comparison of the effectiveness of repository therapy with effectiveness of the usual hyposensitization method of treatment. Although these studies will undoubtedly result in a more efficient means of treating the individual, some researchers claim that all patients do not react in a similar manner to a specific allergenic extract because of the number of individual allergenic components in the extract.

If the treatment is conducted prior to the time of pollination of the plants, it is termed **preseasonal;** if it is maintained throughout the year for some allergies, it is called **perennial;** if the treatment is instituted during the symptomatic period, it is known as **coseasonal** (the least satisfactory method).

Rapid hyposensitization of certain allergic patients in a single day has proved feasible, safe, and highly effective. The method has proved particularly successful with bee and wasp venom allergies. The patient is given small injections every 20 or 30 minutes for at least several hours; immunity is developed in from 10 to 14 days.

The hyposensitization treatment is particularly useful for counteracting allergies caused by inhalants and some contactants. When food allergies are encountered, the patient is advised to avoid the offending food in his diet—"elimination diet." Similarly, a change in environment often provides relief from inhalant allergies. A substitution of foam rubber pillows for feather

pillows frequently ends symptoms that occur on retiring. Because the allergic reaction depends on an antigen-antibody reaction, one can readily see that absence of allergen contact with the tissues of the patient provides satisfactory results.

As previously stated, studies on repository allergens are in progress. For such preparations to be free of ill effects, the antigen must be completely emulsified. A large dose of the antigen, when completely emulsified in an oil and buffered saline solution, is slowly absorbed into the system. One injection may be sufficient for an entire season.

The use of alum-precipitated extracts has also been suggested as a means of therapy. Nondefatted pollen is mixed with pyridine, resulting in extraction of lipid material as well as the water-soluble fraction. Alum is then added, thereby precipitating an antigenic complex. Pyridine and alum are removed by washing, and the precipitate is suspended in buffered saline solution. Alum-precipitated allergenic extracts are administered subcutaneously in the same manner as aqueous extracts and emulsified extracts.

Several advantages are claimed for alum-precipitated extracts: delayed absorption of allergen permits the administration of fewer yearly injections, and treatment permits the administration of larger amounts of the allergen per injection with less possibility of systemic allergic reaction; in addition, extracts are available commercially, suitably standardized, and relatively easy to administer. Allpyral® products are examples of alum-precipitated extracts.

The allergist may elect to administer antihistaminic drugs orally in addition to using the allergenic extract. Although the antihistamines cannot prevent the antigen-antibody reactions, they do prevent the shock damage normally caused by the release of histamine. The pharmacist should be capable of advising the physicians about the many antihistaminic drugs and should know the chemical nature, the therapeutic advantages and disadvantages, and the generic and trademarked names of each drug. The pharmacist, as a drug specialist, should be familiar with the products. Moreover, the pharmacist should warn customers about the potential dangers of continued promiscuous use of the antihistamines during self-medication.

PLANTS CAUSING HAYFEVER

To determine whether certain plants liberate air-borne pollens, one must sample the atmospheric content of the area. The gravity (Durham sampler) method of exposing slides and the roto-rod, roto-bar sampler, fly-shield rotobar, flag sampler, volumetric impinger, Wells air centrifuge, Erdtman air filter, and many other methods have been devised by investigators in the field of aerobiology.

To ascertain whether certain plants are significant in seasonal pollinosis, a series of postulates was devised by authorities in the field of allergy to serve as definite criteria:

1. The pollen must contain an excitant hayfever.
2. The pollen must be anemophilous, or wind-borne, as regards its mode of pollination.
3. The pollen must be produced in suf large quantities.
4. The pollen must be sufficiently buoyto be carried considerable distances.
5. The plant producing the pollen must be widely and abundantly distributed.

The Durham sampler method of determining the pollen count is the gravity method in which a microscope slide is rubbed with a petrolatum mixture (white petrolatum 75%, liquid petrolatum 25%) and is exposed in a standard exposure device (Figs. 14–4 and 14–5) for a 24-hour period. At the end of that time, the slide is examined microscopically by staining

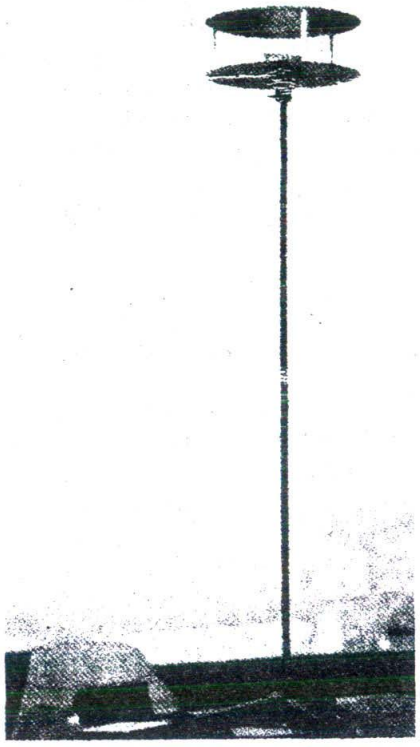


Fig. 14–4. Pollen exposure apparatus in position on roof.

with Calberla's solution,* adding a 22-mm square coverglass, and counting the different kinds of pollen grains under the entire cover glass area. The pollen count represents the number of pollen grains per square centimeter of slide surface.

The chief advantages of the various aforementioned air-sampling devices are the ease of determining hour-by-hour pollen counts and the relationship of pollen occurrence to air volume.

Although such counts have little or no value insofar as individual hayfever sufferers are concerned, they are of great importance in national surveys. When a person wishes to change his place of employment, he can easily learn which parts of the country are relatively free from ragweed or other pollens. For instance, a ragweed hayfever victim should know that Portland, Oregon, is preferable to St. Louis, Chicago, or Milwaukee because the pollen counts in the latter cities are exceedingly high. Again, a vacation at the eastern seashore or at the western national parks may provide a more comfortable time for a person suffering from ragweed allergy.

The American Academy of Allergy, through its Pollen and Mold Committee, has established a chart for the ragweed index of the principal cities.

In the New England, middle Atlantic, central, plains, and Pacific northwest states, the pollinating seasons of trees, grasses, and weeds are rather clearly defined. For example, in the middle Atlantic states, a seasonal hayfever occurring between February 9 and May 20 is undoubtedly caused by pollens from one or more trees, that between May 30 and July 4 is probably owing to grass pollens or to a few early flowering weeds, and that between August 10 and October 1 is undoubtedly the result of ragweed pollens.

Thus, in most of the United States, 3 pollen seasons may be easily differentiated: (1) the spring, or tree season; (2) the early summer, or grass and early weed season; and (3) the later summer-early fall, or true weed season (often referred to as the ragweed season).

Trees

Although some species may overlap, the spring-flowering trees may be subdivided into those of early spring and those of late spring.

Early Spring Pollinating Trees:

Ulmus americana L.
(American elm)
Ulmus rubra Muehlenb.
(slippery elm)

*Calberla's solution: glycerin, 5 ml; alcohol (95%), 10 ml; distilled water, 15 ml; saturated aqueous solution of basic fuchsin, q.s. to a cherry-red color.

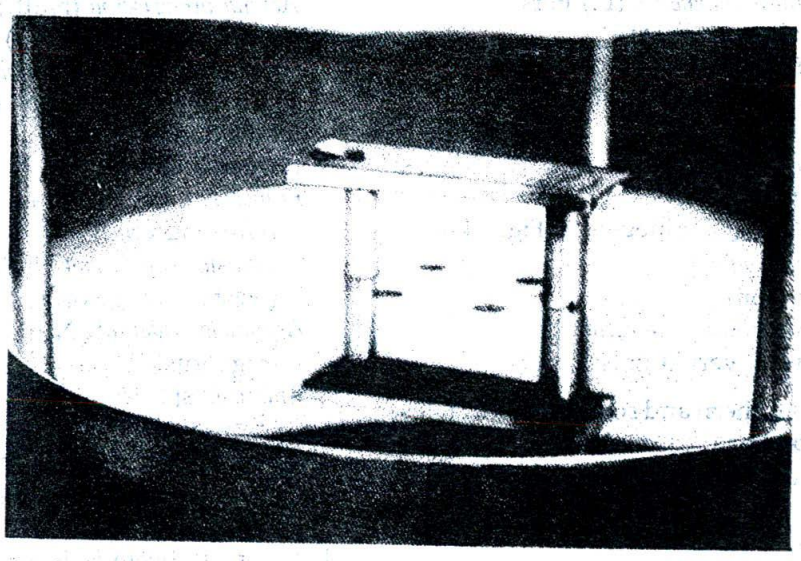


Fig. 14–5. Enlargement of slide holder with slide in place.

Acer saccharinum L.
(silver maple)
Acer rubrum L.
(red maple)
Populus deltoides Marsh.
(necklace poplar)
Populus tremuloides Michx.
(quaking aspen)
Populus canadensis Moench.
(Carolina poplar)
Alnus rugosa (Du Roi) Spreng.
(speckled alder)
Alnus serrulata (Ait.) Willd.
(common alder)

Later Spring Pollinating Trees

Betula papyrifera Marsh.
(paper birch)
Betula lenta L.
(sweet birch)
Broussonetia papyrifera (L.) Vent.
(paper mulberry)
Juglans cinerea L.
(butternut)
Juglans nigra L.
(black walnut)
Quercus alba L.
(white oak)
Quercus rubra L.
(red oak)
Quercus velutina Lam.
(black oak)
Platanus occidentalis L.
(buttonwood)
Platanus acerifolia (Ait.) Willd.
(London plane)

Significant allergenic pollens are liberated also from trees that may not adhere to these time schedules: the Australian pines, *Casuarina* species, common in Florida; the blue gum trees, *Eucalyptus* species, naturalized in California; the Rocky Mountain juniper, *Juniperus scopulorum* Sarg., occurring throughout the Rocky Mountain range; the mountain cedar, *Juniperus mexicana* Spreng., extending into Texas; the orange, lemon, and related species of citrus; and a number of others. It is interesting to note that although pine trees, *Pinus* species, produce considerable quantities of wind-borne pollen, they are not generally considered to be allergenic.

Grasses

The most important grasses of the United States that shed allergenic pollens are:

Cynodon dactylon (L.) Pers.
(Bermuda grass) (Fig. 14–6)

Sorghum halepense (L.) Pers.
(Johnson grass)
Dactylis glomerata L.
(orchard grass) (Fig. 14–6)
Phleum pratense L.
(timothy) (Fig. 14–6)
Poa pratensis L.
(Kentucky bluegrass) (Fig. 14–6)
Agrostis alba L.
(redtop)
Anthoxanthum odoratum L.
(sweet vernal grass)

In the southern and southwestern states, grasses pollinate throughout the year and no particular season is apparent. It is probable that many other grasses are factors in grass pollinosis.

Weeds

Among the early flowering weeds, certain members of the Chenopodiaceae, Polygonaceae, Plantaginaceae, Amaranthaceae, and Compositae are responsible for a number of cases of allergy each year. Other members of these families pollinate later in the summer; in fact, depending on geographic location, they may extend into late fall. *Plantago major* L. (common plantain) and *Plantago lanceolata* L. (English plantain) (Fig. 14–7) are causes of widespread early summer weed pollinosis. Pollen grains of the plantains are rather small, averaging approximately 24 μ, but they are easily identifiable because of the protuberances arising from the exine.

Other important hayfever weeds are:

Rumex crispus L.
(yellow dock)
Rumex acetosella L.
(sheep sorrel)
Chenopodium album L.
(lamb's quarters)
Chenopodium ambrosioides L.
(Mexican tea)
Amaranthus palmeri Wats.
(Palmer's amaranth)
Amaranthus retroflexus L.
(pigweed)
Acnida tamariscina (Nutt.) Wood.
(western water hemp) (Fig. 14–8)
Salsola kali L. var. *tenuifolia* Mey.
(Russian thistle) (Fig. 14–8)
Iva xanthifolia Nutt.
(marsh elder)
Franseria tomentosa Gray
(false ragweed)
Artemisia ludoviciana Nutt.
(western mugwort)
Artemisia tridentata Nutt.
(sagebrush)
Ambrosia species
(ragweeds) (Fig. 14–9)
Kochia scoparia (L.) Schrad.
(burning bush) (Fig. 14–8)

The genus *Ambrosia* is responsible for about 90% of the pollinosis in the United States. Four species are widespread over the eastern, southern, central, and southwestern states. Only the west coast and the Pacific northwest states have ragweed pollen counts ranging from zero to only a few grains. The 2 species that may be found in greatest abundance are the **giant** or **great ragweed** and the **dwarf** or **common ragweed.** Although these vary considerably in height, leaf structure, and general habit, their pollens are practically indistinguishable. They range in size from 18 to 21 μ, are uniformly rounded, are tricolpate, and have a somewhat spiny exine.

Ambrosia trifida L., the giant ragweed, is a coarse annual that sometimes attains a height of 5 meters. The staminate flowers are borne in terminal spikes or racemes, at the base of which are the pistillate flowers. The leaves are oppositely arranged and long-petioled and are usually 3-lobed, although occasionally they are 5-lobed or entire-margined. The lower leaves are generally more uniform in appearance than those on the upper stems. Both stems and leaves are rough to the touch because of the stiff hairs.

Ambrosia artemisiifolia L. var. *elatior* (L.), Descourtils, the dwarf ragweed, is sometimes referred to merely as *Ambrosia elatior*

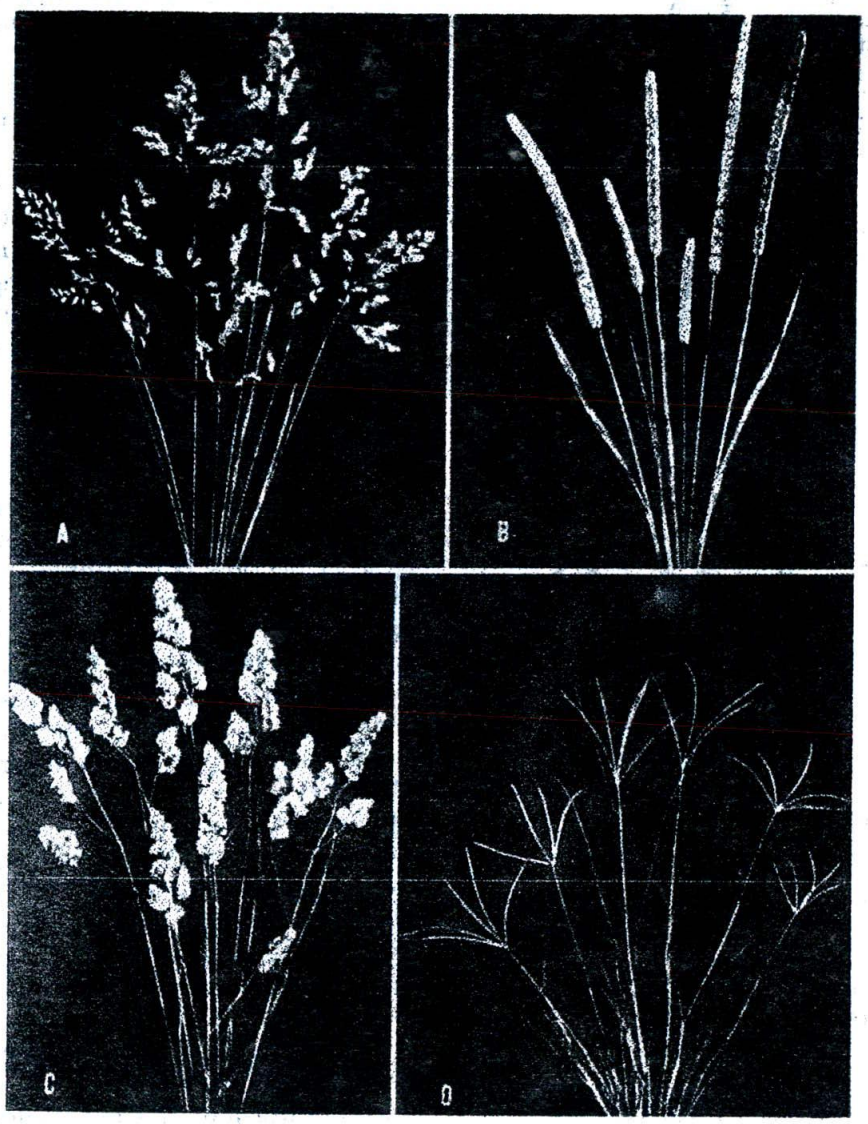


Fig. 14–6. Common hayfever grasses. *A*, bluegrass or June grass; *B*, timothy; *C*, orchard grass; *D*, Bermuda grass. (Feinberg, *Allergy in Practice*, courtesy of Year Book Publishers, Inc., and O.C. Durham.)

L. It is a much-branched annual that occasionally grows 2 meters high. It is characterized by its numerous staminate spikes or racemes and by its fernlike leaves which are bipinnatifid. The leaves are extremely variable and sometimes those of the flowering branches are undivided. As a rule, the leaves are alternate, and like the giant ragweed, the plant is hairy. Both of these ragweeds occur chiefly in the northeastern, middle Atlantic, and central states.

In the southern and western plains states, *Ambrosia bidentata* Michx., the southern ragweed, is an important species. It has alternate leaves that are lanceolate, partly clasping, and nearly entire except for a short lobe on each side near the base. In the western and southwestern states, *Am-*

Fig. 14–7. English plantain. (Tuft, *Clinical Allergy*, Lea & Febiger.)

brosia psilostachya DC., the western ragweed, is the most abundant species. It is a branched perennial with thick 1-pinnatifid leaves; the plant is rough and hoary with short stiff hairs.

MOLDS CAUSING ALLERGY

Mold allergy is an exceedingly important cause of perennial rhinitis or nonseasonal hayfever. Atmospheric determinations conducted in much the same manner as pollen counts have revealed that the most common mold genera are *Alternaria* (Fig. 14–10), *Macrosporium*, *Helminthosporium*, *Hormodendrum (Cladosporium)*, *Aspergillus*, *Penicillium*, *Mucor*, *Rhizopus*, *Syncephalastrum*, *Curvularia*, *Brachysporium*, *Pullularia*, *Pleospora*, and others. Because of the difficulty in distinguishing between the spores, it is helpful to expose Petri dishes containing a mycologic medium specifically designed to encourage the growth of molds and yeasts but to inhibit bacterial colonies. Thus, each colony of the mold that develops is assumed to be the outgrowth of one spore; the vegetative characters of the mycelium and the methods of sporulation are employed to aid in identification of the mold. It is interesting to note that present investigators hold the imperfect fungi chiefly responsible for mold allergies.

PLANTS CAUSING DERMATITIS

Rhus toxicodendron or poison ivy is composed of the fresh leaflets of *Toxicodendron radicans* (L.) Kuntze, formerly known as *Rhus radicans* L. (Fam. Anacardiaceae), a woody vine common throughout the United States. The plant either trails over the ground, climbs by means of aerial roots, or remains shrublike. The common climbing type is shown in Figure 14–11. The leaves are 3-foliate, and the leaflets are ovate, acuminate, nearly entire, inequilateral, 3 to 20 cm long, and have short stalks. They are inodorous and slightly astringent, saline, and acrid in taste. The flowers are green and occur as loose axillary panicles. The fruit is a globular, glabrous, grayish drupe.

The active principle of poison ivy, and of other *Toxicodendron* species as well, is known as **urushiol**. It is not a single compound but, instead, a mixture of closely related C_{15} and C_{17} catechols, varying from one another by the number and position of double bonds in their side chains. Urushiol from poison ivy is made up mainly of pentadecylcatechols, but heptadecylcatechols are also present. The toxic constituents of poison oak, on the other hand, are mainly heptadecylcatechols accompanied by some pentadecylcatechols.

Urushiol occurs in the sticky sap of the plant that exudes when the plant is injured. It causes dermatitis on penetration

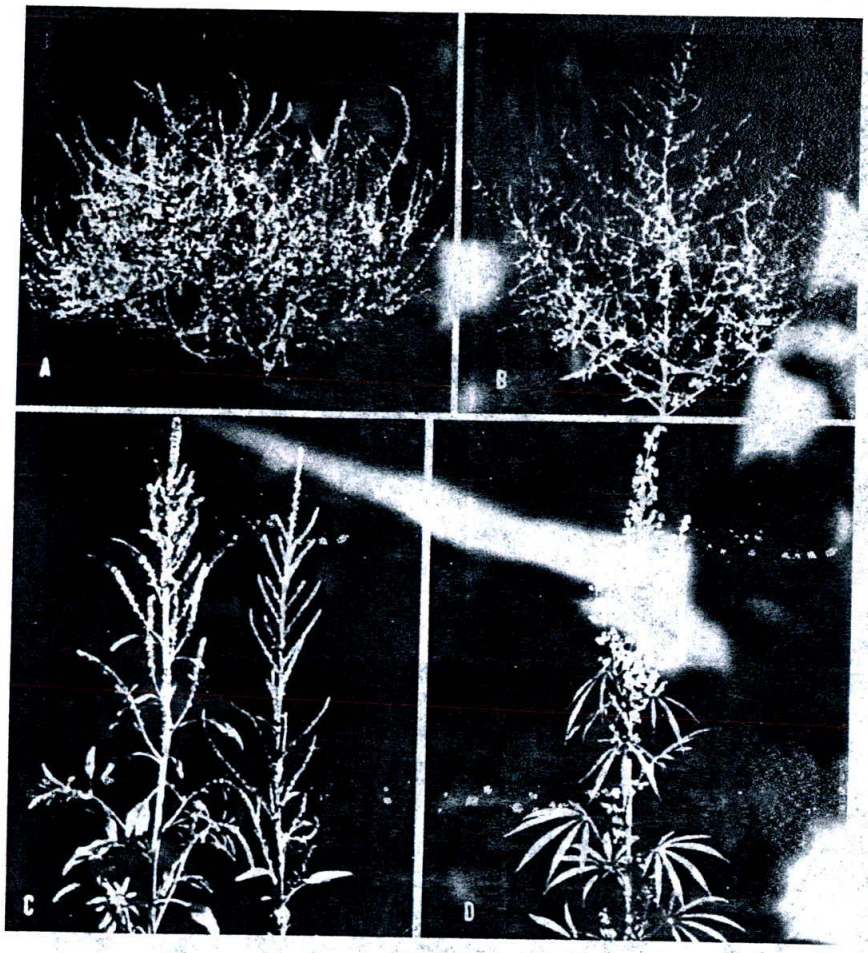


Fig. 14–8. Hayfever weeds of midwestern and western states. *A*, Russian thistle; *B*, burning bush or Mexican fireweed; *C*, western water hemp; *D*, hemp or marihuana, not related botanically to western water hemp. (Feinberg, *Allergy in Practice*, courtesy of Year Book Publishers, Inc.)

of the epidermis of the skin. It may be conveyed by the hands or clothing from one person to another. Also, it can be transmitted readily from place to place by different carriers, both animate and inanimate. Shoes, gloves, and clothing can retain the toxicity of urushiol for months. Dogs, cats, and farm animals frequently become contaminated, and their hairs may be the source of human contamination. Smoke from brush fires may carry leaf particles; such particles can produce cases of ivy poisoning when they contact the human skin.

Urushiol is not infective and apparently does not enter the blood. Minute quantities (0.001 mg) on the epidermis can cause dermatitis.

Toxicodendron vernix (L.) Kuntze, commonly known as **poison sumac, poison elder, or poison dogwood,** is allergenic, like *Toxicodendron radicans*, and contains similar active principles. It is a shrub or small tree found in swamps in the United States and Canada (see Fig. 15–6). The leaves are 7- to 13-foliate, with obovate or oval acuminate, entire leaflets; the flowers are small and green, and in axillary panicles; the fruit resembles that of poison ivy.

Other species of *Toxicodendron* are also

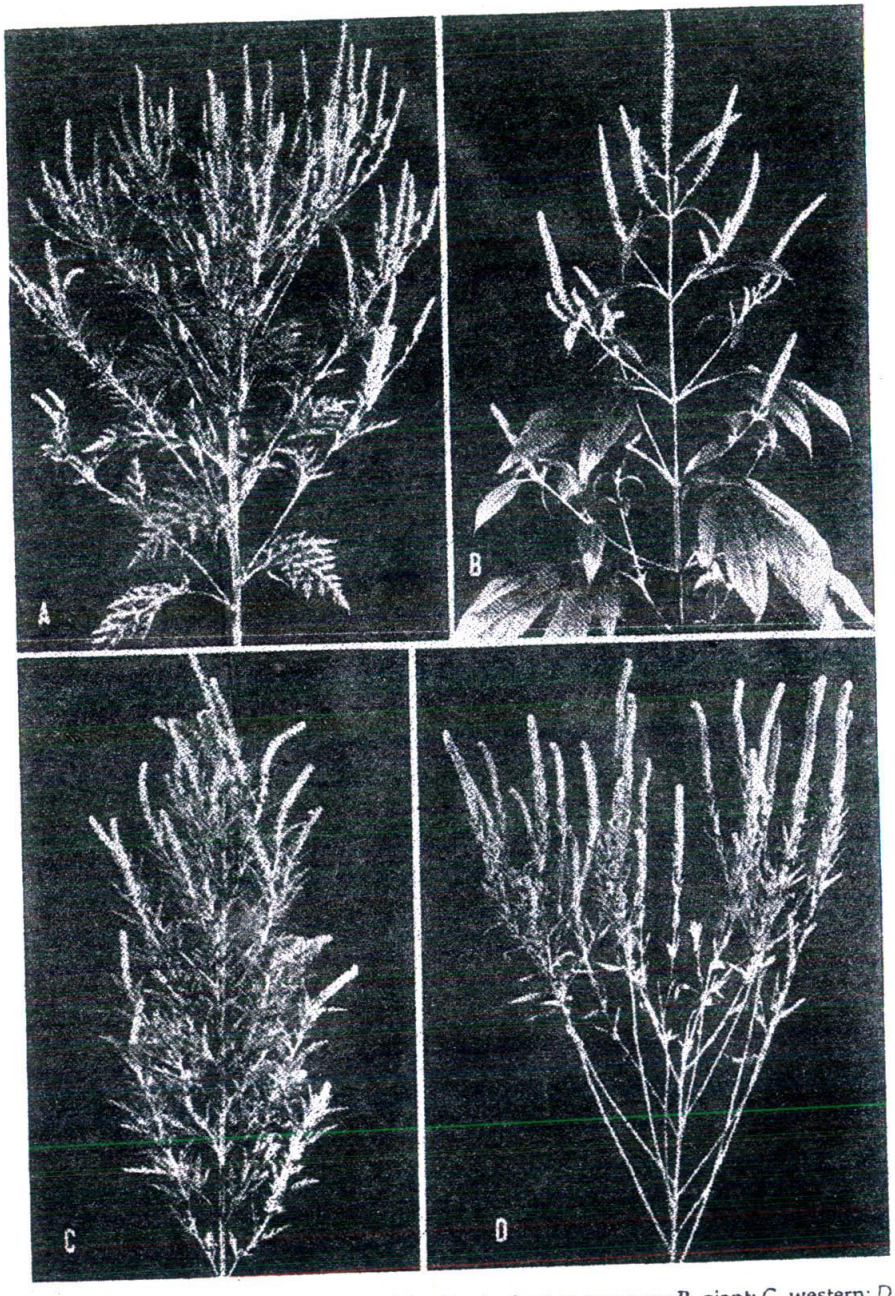


Fig. 14–9. Prominent members of the ragweed family. *A*, short or common; *B*, giant; *C*, western; *D*, southern or lanced-leaved. (Feinberg, *Allergy in Practice*, courtesy of Year Book Publishers, Inc.)

Fig. 14–10. Alternaria spores seen on exposed slide. (Tuft, *Clinical Allergy*, Lea & Febiger.)

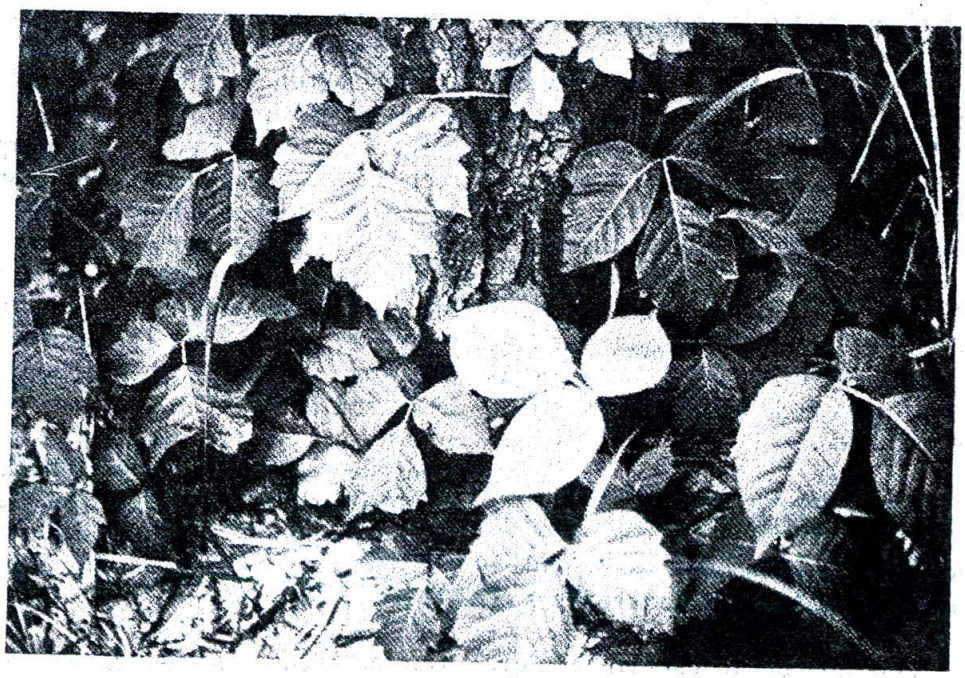


Fig. 14–11. Variation in the leaflets of poison ivy *(Toxicodendron radicans)*. The lobed leaflets are sometimes called poison oak.

poisonous, as the **western poison oak** *(T. diversilobum)* of the Pacific coast, and the **Japanese lacquer** or varnish tree *(T. verniciferum)*. The lacquer trees grow wild in both China and Japan, where they are also cultivated. The specific name *vernix* means "varnish." The lac is obtained by incising and removing the bark with a pointed spatula. The grayish-white emulsion, which contains urushiol, is strained and, when exposed to air, changes to brown and finally becomes black. This change is brought about by the oxidizing enzyme, laccase.

In a series of tests on thousands of student volunteers, injections of 3-pentadecylcatechol (one of the constituents of urushiol) reduced sensitivity to poison ivy dermatitis and created immunity in some cases. The compound is a standard allergen used in patch tests to determine sensitivity to the poison ivy plant.

One of the products developed for the prevention and treatment of poison ivy dermatitis is an alum-precipitated, pyridine extract of *Toxicodendron radicans*. This product is, in reality, a purified extract of urushiol suspended in isotonic saline solution and is intended for subcutaneous administration. The antigen is slowly absorbed, thereby providing a continuous stimulation of antibodies for a long period of time. It should be stored at a temperature of between 2 and 10° C. Commercial products consisting of urushiol from 1 or more species of *Toxicodendron* include Aqua Ivy®, Rhus Tox Antigen®, and Rhus-All Antigen®. Oral preparations, such as ImunOak® and Ivy-Safe®, are also said to be effective in building immunity against rhus dermatitis.

OTHER CAUSES OF ALLERGY

No treatise on allergy would be complete without a consideration of other types of allergic conditions, such as **bacterial allergy, drug allergy, atmospheric allergy, occupational allergy, physical allergy,** and **psychosomatic allergy.** Because all of us are in daily contact with microorganisms, both externally and internally, it is not unthinkable that persons may become sensitized to bacteria. Indeed, it is difficult to distinguish between some forms of bacterial infections, particularly of the nasal and bronchial mucosa, and some forms of bacterial allergy.

Many drugs produce an allergic response in hypersensitive individuals. Penicillin allergy has already been discussed on page 422, and sensitivity to biologics prepared from horse serum has been mentioned on page 405. Numerous other drugs elicit symptoms characteristic of inhalant, ingestant, injectant, and contactant allergens.

Acetylsalicylic acid may cause allergic manifestations not only in hypersensitive patients who ingest it but also in susceptible community pharmacists who may use it in compounding. It may affect manufacturing pharmacists who work with it in quantity in formulating medicinal products. Frequently, the aspirin produces lacrimation and sneezing; occasionally, it causes dermatitis. Cases are recorded of allergic reactions to trypsin, insulin, sulfa drugs, antibiotics, and even to antihistamines and cortisone!

The primary cause of physical allergy is problematic, although conceivably shock tissues are involved. Cold water, extreme pressure, or other conditions may produce erythema or configurations on the skin. Medical records indicate that emotional complexes of children and adults may produce certain types of allergies; often extreme anger, sorrow, or jealousy will be sufficient cause for asthma, dermatitis, or other allergies to become apparent. It is not definitely known if these allergies are the result of specific antigen-antibody reactions.

It is believed that one allergy may potentiate the action of another. A person who can tolerate ragweed pollen without sneezing may begin such a reaction only

after eating allergenic foods such as shrimp or chocolate bars. Similarly, a person who normally suffers no gastrointestinal allergy after eating tomatoes may develop diarrhea, extreme abdominal pain, or exhibit a skin rash during a certain pollinating season.

The subject of allergy is exceedingly complex, but by the same token, it is usually interesting. The future holds the answer to the cause of allergenic reactions and their prevention and cure.

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