Angioneurotic edema is manifested clinically by sudden swellings of the skin or mucous membranes, which persist for a few hours to several days, and disappear as quickly as they come. There may be only a single outbreak during the life of an individual or the swellings may occur at irregular intervals with greater or less frequency, so that in some cases the life of the victim may become burdensome. In some cases the attacks are periodic. The size of the swellings varies, at times being enormous. In certain positions they may cause death by mechanical interference with one of the vital functions. This is most common in edema of the glottis.

The disease may appear in childhood or it may not be noticed until past middle age. Usually it becomes less annoying as old age approaches.

In the past the causes of the disease were given by various authors as “nervous influences,” “infections,” “disorders of the endocrine glands,” and “dietetic errors.” At present allergy would seem to be the most plausible explanation and this is substantiated in certain types of the disease. Whether allergic individuals are born hypersensitive to specific substances, or whether they are born with a tendency to become easily sensitized is still a much disputed subject. Coca (1920) is quite positive that, unlike experimental anaphylaxis, it is not an antibody-antigen reaction. On the other hand, Schloss (1920) reports the passive transference of sensitization from children to guinea-pigs by means of the blood serum.

However this may be, it is known that in some cases the ingestion of certain foods causes the attack and that when these foods are not eaten, the attacks do not occur, and that in many of these, but not all, a positive skin test to the protein of the offending food can be demon-
strated. In some cases where the skin tests are positive to specific foods, abstinence from them does not always prevent the attacks. In others the disease may be shown clinically to depend on a food and the skin test to it may be negative even though its removal from the dietary apparently prevents the outbreaks.

From a clinical standpoint these definitely allergic cases may be roughly grouped into two types which we will designate as the prompt and the delayed.

In the prompt type within a comparatively short time after the offending protein is taken, nausea, vomiting, and perhaps diarrhoea, appear, and these are quickly followed by areas of pruritis and wheals which rapidly coalesce. The edema soon assumes remarkable proportions especially about the head and neck. Skin tests are often positive. Adrenalin may be potent to control the attack. In many individuals some of the outbreaks never go beyond the urticarial stage, while others become edematous.

This type of angioneurotic edema closely resembles certain cases of general allergic reaction which are produced in hypersensitive individuals when they are injected with the various substances to which they react. (Walker 1918; Cooke 1922.)

In the delayed type some hours or even days may elapse after the ingestion of the offending food before symptoms appear. The lesions are usually single and commence with a slight tingling or pricking sensation, and expand with remarkable speed until they become superwheals. Gastro-intestinal crises may or may not be present. Adrenalin, even when injected into the swellings, is apparently valueless in controlling them. As a rule, skin tests are negative, but there are exceptions, so that the determination of the offending substance rests upon a clinical basis only. For this reason the cause of the disturbance is not ascertained in many cases which are definitely hypersensitive; consequently, their treatment is unsatisfactory and difficult.

Osler (1897) suggests that changes occurring in the food during some stage of its sojourn in the body may be responsible for some of these cases.

Since the time of Quincke (1882) angioneurotic edema has been recognized as heritable, and indeed many authors state that it seems to be a Mendelian dominant, but we know of no one who has made an analysis of the reported families. From a genetic standpoint the disease can be classified as sporadic and familial.
Sporadic Angioneurotic Edema

The so-called sporadic cases deserve minute investigation. Allergy is certainly the fundamental condition in most of them, and the family history often reveals the presence of eczema, urticaria, hay-fever, asthma, etc. An example of this is shown in figure 1 (PHILLIPS 1922). Indeed, its association with these diseases, which also depend upon allergy, is so common as to suggest the possibility that the heredity of these diseases depends upon more than one factor.

![Figure 1](https://example.com/figure1.png)

**Phillips' Case**

- 

$\square =$ angioneurotic edema  

$\text{As} =$ asthma  

$\text{Ec} =$ eczema  

$\text{Ha} =$ hayfever

Figure 1.—From PHILLIPS (1922), illustrating a sporadic case in which eczema and asthma are familial traits. Note that in this family all males are affected with some manifestation of sensitization.

It may be noted here that the visible lesions of allergy are those of hyperemia and edema. Thus in the skin test (BROWN 1922) a positive result is shown by erythema followed by the formation of a wheal, with irregular outlines and pseudopod-like extensions of the edema, which apparently follow the course of the lymphatics. In the erythemas the hyperemia is more noticeable than the edema. These conditions are reversed in urticaria. Hay-fever is characterized by the development of a similar hyperemia and edema of the mucous membranes of the eye, nose and throat. However, the appearance of this edema is somewhat modified by a secondary bacterial infection of the swollen mucous membrane. Certain types of eczema would seem to show a like series of changes.
occurring in the skin. These are further complicated by trauma, inflicted by the patient as he scratches his itching skin, and by secondary infection.

Most authors consider asthma due to a spasm of the non-striated muscle of the bronchi, but the appearance of the mucous-membrane lining of the trachea and bronchi, as described by Freudenthal (1912) who viewed them through the bronchoscope during attacks, would seem to show definitely that here again we have erythema and edema of the mucous membrane.

The rheumatoid pains so often associated with urticaria and angioneurotic edema, are probably due to a similar condition of the serous membrane of the joints.

In angioneurotic edema this edema seems to be more generalized and intense, so that the skin, mucous, and serous membranes, and their underlying connective tissues, are all affected.

As all of these diseases are well known to be heritable, and are often associated as family traits, it would seem that the main difference between them lies in the distribution of hypersensitive tissues and in the intensity of their reaction. The cause of these patterns of distribution of hypersusceptibility of the tissues and the variation in its intensity should be investigated by the geneticist.

The solution is rendered difficult not only because the hypersensitivity is not specific, as various members of the same family respond to different proteins, but also on account of the varying age at which symptoms appear. Cooke and VanderVeer (1917) have called attention to the fact that symptoms occur earliest in those individuals who inherit this tendency from both parents. They consider allergy as a dominant trait while Adkinson (1920) investigating the heredity of asthma as a specific disease, concluded that it was a recessive.

Another of the many difficulties is that a person may be hypersensitive, but, unless the environment is such that he comes in contact with his allergic substance, he will remain ignorant of his condition. Thus we know of one family of Germans in which ragweed hay-fever appeared for the first time in many of its members the very first fall after immigrating to this country, those afflicted ranging in age from the grandfather to a young child. Such persons might easily appear in a pedigree as normals.

Despite all these obstacles we believe that full pedigrees of victims of angioneurotic edema of the sporadic type from hypersensitive families, including all normal members as well as those afflicted with the various clinical types of allergy, might aid much toward unraveling this mystery.
FAMILIAL ANGIONEUROTIC EDEMA

In the familial types the attacks appear generation after generation in many members of the afflicted families and exact a heavy toll of suffocative deaths caused by edema of the glottis. These characteristics are shown in figure 2. The symptoms are so like those occurring in the sporadic type that it is generally considered to be an identical condition, but we are not aware of the skin reactions of any of these families having been made the subject of research by the immunologist. Studies of the protein reactions in one of these families, together with a complete family history covering all diseases of allergic origin, might do much toward solving the problem of the heredity of human allergy.

A careful study by matings of the twenty-seven pedigrees published in the Treasury of Human Inheritance (BULLOCK 1909), which appears to bring the data up to its date, together with the pedigrees of BOLTEN (1919), CAMERON (1920), CROWDER and CROWDER (1917), and EDGERLY and LUSK (1919), which have been published later, has been summarized in tables 1 and 2.

<table>
<thead>
<tr>
<th>charactaristics of progeny</th>
<th>male parent affected, 56 matings</th>
<th>female parent affected, 46 matings</th>
<th>summary 102 matings</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>offspring</td>
<td>percent</td>
<td>offspring</td>
</tr>
<tr>
<td>affected males</td>
<td>70</td>
<td>35</td>
<td>29</td>
</tr>
<tr>
<td>affected females</td>
<td>45</td>
<td>22.5</td>
<td>21</td>
</tr>
<tr>
<td>unaffected males</td>
<td>47</td>
<td>23.5</td>
<td>27</td>
</tr>
<tr>
<td>unaffected females</td>
<td>17†</td>
<td>17†</td>
<td>10†</td>
</tr>
<tr>
<td></td>
<td>38</td>
<td>19</td>
<td>28</td>
</tr>
</tbody>
</table>

*Including those of unknown sex.
†Sex unknown.

From tables 1 and 2 it will be seen that only two types of matings occur in the pedigrees, namely, matings of affected individuals with unaffected and matings of unaffected with unaffected. Taking up the matings of affected × unaffected first (table 1), the figures show conclusively that familial angioneurotic edema may be transmitted by either parent equally well, the disease appearing in approximately half of the offspring. When the male parent is the one affected the proportions of
Figure 2.—From Crowder and Crowder (1917), illustrating a typical familial angioneurotic edema. Note the high mortality due to glottis edema.
affected are larger than would be expected. This difference is in the opposite direction when the female is the affected parent. Affected males are more numerous than affected females. This is what one would expect since males are more numerous in the whole population. However, the excess of affected males over unaffected males \((99 - 74 = 25)\) is considerable when compared with the females among which the affected and unaffected are equal in numbers. Many authors still consider human sensitization as an expression of anaphylaxis. If familial angioneurotic edema proves to be due to allergy, this type of inheritance forms a striking contrast to the so-called inheritance of laboratory anaphylaxis in which the offspring of the females only are affected because the sensitization is due to a passive transfer of antibodies. If table 1 were our sole source of material we would say without hesitation that angioneurotic edema is a dominant trait and that all matings recorded in the table were of the DR \(\times\) RR type, giving DR and RR offspring in equal numbers. The

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**TABLE 2**

*Neither parent affected.*

<table>
<thead>
<tr>
<th>CHARACTERISTICS OF PROGENY</th>
<th>PRODUCING NO AFFECTED PROGENY</th>
<th>PRODUCING AFFECTED PROGENY</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>One grandparent* affected</td>
<td>One grandparent affected</td>
</tr>
<tr>
<td></td>
<td>27 matings</td>
<td>10 matings</td>
</tr>
<tr>
<td>Affected males</td>
<td>0</td>
<td>12</td>
</tr>
<tr>
<td>Affected females</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Unaffected males</td>
<td>32</td>
<td>6</td>
</tr>
<tr>
<td>Unaffected females</td>
<td>49</td>
<td>3</td>
</tr>
</tbody>
</table>

*In one mating the great-grandparent only was affected.

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**Edgerly and Lusk's Case**

**Figure 3.**—From Edgerly and Lusk (1919), illustrating two unaffected brothers mated to unaffected females, each producing affected offspring.
matings recorded in table 2 throw considerable doubt on this interpretation.

For the sake of ease in analysis table 2 is divided into two parts according to the progeny. The second of these groups is again divided on the basis of whether the grandparents were affected or were unknown. The second category probably belongs with the first, but since nothing is known about the grandparents it is of little value. The results recorded in the first column of the table show that we are here dealing with parents which are recessives, i.e., normals, the matings being of the type RR × RR giving RR offspring only. This is what would be expected if the trait were a dominant. Each of the ten matings recorded in the next column produced affected individuals. These with the six matings of the next column indicate that in sixteen out of a total of forty-three matings, or 37 percent, the parents carried the trait without showing it. These figures are too large to be due entirely to accidental errors.

Two other explanations are possible; firstly, that angioneurotic edema is due to a fundamental condition which requires some specific stimulus to disclose it and that these cases were potentially affected but were not exposed to the proper stimulus to make the disease appear; or secondly, that the condition is due to two factors which are closely linked. If the second explanation is the correct one, each of two unaffected parents supply one of these factors, which after crossing over are transmitted together more often than they are separated. This would account for their inheritance in most cases as a dominant trait. It would also account for the occasional production of an affected individual from two unaffected parents each alone incapable of producing edema. One of these fac-

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**Figure 4.**—From Cameron (1920), illustrating the typical dominant type of inheritance through two double matings.
tors may very likely be the factor which makes the bearer respond to some exciting substance by developing asthma, eczema, hay-fever, or urticaria. The other factor, if such is present, is either similar to the first or unknown. That urticaria, asthma, eczema, hay-fever and other allergic conditions are very common in families where angioneurotic edema occurs has long been known. Sometimes angioneurotic edema and asthma are found together in the same person as in BOLten's (1919) case, figure 5. In this case the patient had angioneurotic edema, urticaria, perennial hay-fever and tetany, while a cousin had angioneurotic edema and asthma.

Bolten's Case

Figure 5.—From Bolten (1919), illustrating familial angioneurotic edema associated with other manifestations of allergy.

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