FIVE GENERATIONS OF ANGIONEUROTIC EDEMA*

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What we now call angioneurotic edema was first adequately described by Quincke,[1] in 1882, as "acute circumscribed edema of the skin." He looked on it as a vascular neurosis and attempted to separate it clinically from all other forms of local edema as a distinct disease. But while to Quincke belongs all the credit of having first presented the subject with the detail and interpretation necessary to its general recognition, he was not the first to observe the condition so carefully as to recognize its individual character. This had been done ten years earlier by Milton,[2] who recorded his observations in 1876 under the title, "On Giant Urticaria," pointing out clearly that the cases were of a new kind to him and were distinctly different from the severest forms of urticaria as previously described and commonly understood. Had he dignified with a new name the new condition he observed so carefully, the recognized literature of angioneurotic edema would no doubt have begun with him.

The nomenclature of angioneurotic edema has been a various one. It has been described under no less than twenty more or less appropriate descriptive titles, such as "giant urticaria," "massive urticaria," "ephemeral congestive tumors of the skin," and "ephemeral cutaneous modosities," while many have called it simply Quincke's disease or Quincke's edema, out of compliment to its discoverer. The term angioneurotic edema was originated by Strübing[3] in 1885, and has been the one most commonly used to designate the condition since that time; though perhaps the most extensive reviewer of the subject, Cassirer,[4] discards it for the simpler one of "acute circumscribed edema," recognizing that there is no final proof of its neurotic origin, that the disease is not confined to the skin, and believing that the name should carry a

* Submitted for publication June 15, 1917.

1. Quincke: Monatsh. f. pract. Dermat., 1882, **1,** 129.
2. Milton: Edinburgh Med. Jour., December, 1876, p. 513.
3. Strübing: Ztschr. f. klin. Med., 1885, **9,** 381.
4. Cassirer: Vasomotorische trophischen Neurosen, p. 242. S. Karger, Berlin, 1901; Lewandowsky's Handbuch der Neurologie, **5,** 256. J. Springer, Berlin, 1914.

distinction from some ill-understood but possibly related chronic edemas like Milroy's disease and recurrent hydrops of the joints.

Angioneurotic edema is not an uncommon disease. In 1901 Cassirer was able to collect from the literature 160 cases, described under one or another of its various names, and many others have been published since. The disease is characterized by acute, massive, ephemeral swellings of the skin, and sometimes of mucous membranes or of internal organs, which often develop and disappear with great rapidity, leaving no trace behind them. It has a tendency to recur, many of those who suffer from it being repeatedly attacked. It is often associated with other neuroses; and it seems to be more or less closely related to urticaria and other skin lesions exhibiting local vascular disturbances. Osler calls its swellings "only urticarial wheals 'writ large,'" but the typical Quincke's disease, with its large, pale, cool, nonitchy swellings, is in marked contrast to the usual form of urticaria; and unlike urticaria the character of the food seems unimportant as an etiologic factor.

Angioneurotic edema generally appears as an acute sporadic affection without adequate clinical explanation. But as a relative rarity there has been observed a familial type of the disease, in which the affection has seemed to be distinctly hereditary and has appeared in several or many members of a family through two or more successive generations. It is to this type of the disease, the general features and literature of which were well summarized by Fairbanks,[5] in 1904, that we wish to direct attention.

Shortly after the identification of Quincke's edema in 1882, Dinkelacher,[6] one of Quincke's students, observed the disease in a watchmaker who had been affected by transient local swellings for many years and who had a son likewise affected from an early stage of infancy. Three years later Valentin[7] observed in this same family another son, not born at the time of Dinkelacher's report, who was affected from the first week of his life, and a daughter who was free from the disease. In 1885 Strübing[8] described a case in a man aged 71 years, who had been subject to attacks of swelling of the throat and face from his 26th year, and who had a son and a daughter similarly affected from very early life. A year later Falcone[9] reported

5. Fairbanks: Am. Jour. Med. Sc., 1904, **127,** 877.

6. Dinkelacher: Inaug. Diss., Kiel, 1882. Reference by Fairbanks, loc. cit., Footnote 5.

7. Valentin: Berl. klin. Wchnschr., 1885, **23,** 150.

8. Strübing: Ztschr. f. klin. Med., 1885, **9,** 381.

9. Falcone: Gazz. d. osp., 1886, **7,** 125. Reference by Fairbanks, loc. cit., Footnote 5.

a case of acute recurring edema in a child of 7 years whose grandfather suffered similar attacks.

Osler[10] first called attention to the existence of hereditary angioneurotic edema in this country, in 1888. He published the history of a family in which it was present through five generations, and in which twenty-two members had suffered from repeated attacks of the disease. Long after the publication of his original report, Osler[11] had the opportunity of examining two members of the sixth generation of this family who also had the disease. The condition was characterized by the occurrence of transient local swellings in various parts of the body which were almost always accompanied by gastro-intestinal disturbances, such as colic, nausea, vomiting and sometimes diarrhea.

Others who have added to the list of cases of the familial type of angioneurotic edema are: Kreiger[12] who, in 1899, reported cases in a mother and son; Fritz,[13] 1893, who recorded a history in which eight members of one family were subject to severe attacks, and five of whom died of edema of the glottis; Roy,[14] 1894, who observed the disease in a mother and daughter; and Ricochon,[15] 1895, who saw three generations of one family affected, the attacks being accompanied by colic, vomiting and fever. Yarian,[16] in 1896, described a case in a woman of 42, with a history of nine other cases among relatives; Schlesinger,[17] 1898, reported on a family which was affected through four generations; Griffith,[18] 1902, saw a father and daughter who died of the disease, with acute edema of the larynx, at the respective ages of 29 and 23; Harris,[19] 1905, observed the disease in a patient aged 21 years, who had twice been tracheotomized for laryngeal edema (which ultimately proved fatal) and whose mother and sister were likewise affected; and Harbitz,[20] 1911, described a case where there was a history of similar attacks in a brother, the father, the paternal grandfather, and in two sisters of the grandfather.

Unusual and extensive were the ravages of the disease in a family observed by Ensor,[21] where among eighty members in three gen-

10. Osler: Am. Jour. Med. Sc., 1888, **95,** 362.
11. Osler: Modern Medicine, Ed. 2, 1915, **4,** 998.
12. Kreiger: Meditzinskvie Oborzrenie, 1889. Reference by Fairbanks, loc. cit., Footnote 5.
13. Fritz: Buffalo Med. and Surg. Jour., 1893-1894, p. 286.
14. Roy: Med. Rec., New York, 1894, **66,** 42.
15. Ricochon: Semaine méd., 1895, p. 365.
16. Yarian: Med. News, London, 1896, **69,** 238.
17. Schlesinger: Wien. klin. Wchnschr., 1898, No. 14, p. 335.
18. Griffith: Brit. Med. Jour., 1902, **1,** 1470.
19. Harris: Am. Jour. Med. Sc., 1905, **130,** 382.
20. Harbitz: München. med. Wchnschr., 1911, **58,** No. 48.
21. Ensor: Guy's Hosp. Rep., 1904, **58,** 111.

erations thirty-three were attacked and twelve died of edema of the glottis.

Unless other and more extensive reports have escaped our notice, it would seem that the opportunity to observe angioneurotic families and to study the history of their trouble through successive generations does not often come to physicians. The history of such a family which has come under our observation may therefore be of sufficient interest to warrant its publication.

In the community where one of us (J. R. C.) resides there has been for many years a family in which the frequent occurrence of local swellings in various parts of the body is a fact of common knowledge to their friends and neighbors and a matter of grave concern to the parents of children who may become victims of this hereditary weakness. Many of the members of this family have suffered severely and repeatedly through longer or shorter lives, and not a few have finally died the victims of attacks in vital organs. The disease is known to have continued through five generations.

Only one of the affected members of this family has come under our personal observation as a patient. He is now nearly 80 years of age. Since early life he has been subject to severe attacks of local edema, sometimes of monstrous size, developing quickly, disappearing with equal rapidity, and affecting at different times practically all parts of the surface of the body. In his later years these attacks have been infrequent and of slight severity, but through all of his early adult and middle life they were both frequent and severe. He was never able to foretell them more than a very short time before the swelling began, and was never able to associate them with any particular event, either dietary, traumatic, or otherwise. They come out of nowhere, and disappear with equal mystery. There is sometimes disturbance of the digestive system, but it has no constancy. He says that before the swelling begins there may be a little tingling or burning, but rarely a genuine pain, and that with full development there is only a local feeling of fulness and tension. With the attacks there is always a sense of anxiety and uneasiness, and a fear born of painful knowledge of misfortune in many of his relatives that the trouble will "strike to the throat." There is a family tradition that the immediate adoption of heroic treatment with alcoholics and nitroglycerin will combat the cause and cure the attack. And, indeed, it has seemed to do so many times; but whether the relation of cause and effect is properly judged in this there would seem to be much doubt.

The family history, in so far as it concerns the appearance of angioneurotic edema, begins with the father of our patient. About 1820, being then a young man and recently married, J. C. took a contract in the logging camps of western Pennsylvania. The winter was very cold, with much snow on the ground, and he lived under the primitive conditions to be found in loggers' cabins. During this winter he had an attack of illness which was subsequently referred to as quinsy, in which the neck was greatly swollen. From that time on swellings were repeated at irregular intervals, invading all parts of the body, and they were eventually fatal through involvement of the throat, though not until the lapse of something like twenty years. Previous to his attack in the logging camps he had never suffered with any such malady, nor, so far as was ever known to him, was there any history of a similar affection in his immediate family or among any of his relatives.

This man was the father of ten children, three daughters and seven sons, of which our patient was next to the youngest. Though the mother of these children was entirely free from their father's affliction, his peculiar malady was transmitted to all of them with the exception of one son, and seven of them are said to have died of the disease. Two of the affected nine of the

second generation died without descendants; to the remaining seven there were born twenty-nine children, and twelve of these twenty-nine had angioneurotic edema. In only one of the seven groups of children born to these seven affected parents, and making up the third generation, were all the children free from the disease. In the fourth generation there are seven known groups of children with a total of eighteen individuals. Nine of these children are descended from three unaffected parents and are free from the disease. Nine are descended from four affected parents and five have the disease. Only one of the affected parents gave issue to children who have thus far entirely escaped. The fifth generation contains only six known members up to the present. Three are the daughters of an unaffected mother and are free from the disease; three are the daughters of an affected mother, and one of them has the disease—the only case so far observed in the fifth generation.

In this family, so far as it can be traced from the first to the fifth generation, definite histories have been obtained of sixty-four individuals. Among them there have been twenty-eight cases of angioneurotic edema and fifteen deaths from an acute form of the disease. That is, of the sixty-three known descendents of J. C. twenty-seven, or 42.9 per cent., have inherited his disease, and 51.5 per cent. of those who have had the disease have died of it. Both the descendents of J. C. and the cases of angioneurotic edema among them have been about equally divided between males and females. Of the former there have been thirty-two, with thirteen, or 40.6 per cent., affected; of the latter there have been thirty-one, with fourteen, or 45.2 per cent., affected. Their distribution by generations is shown in Table 1.

TABLE 1.—DISTRIBUTION BY GENERATIONS

Generation		Males	Females	Total
II	Affected	6	3	9
	Not affected	1	0	1
	Per cent. affected	85.6	100.0	90.0
III	Affected	5	7	12
	Not affected	12	5	17
	Per cent. affected	34.0	58.4	41.4
IV	Affected	2	3	5
	Not affected	6	7	13
	Per cent. affected	25.0	30.0	27.8
V	Affected	0	1	1
	Not affected	0	5	5
	Per cent. affected	....	16.6	16.6
Total	Affected	13	14	27
	Not affected	19	17	36
	Per cent. affected	40.6	45.2	42.9

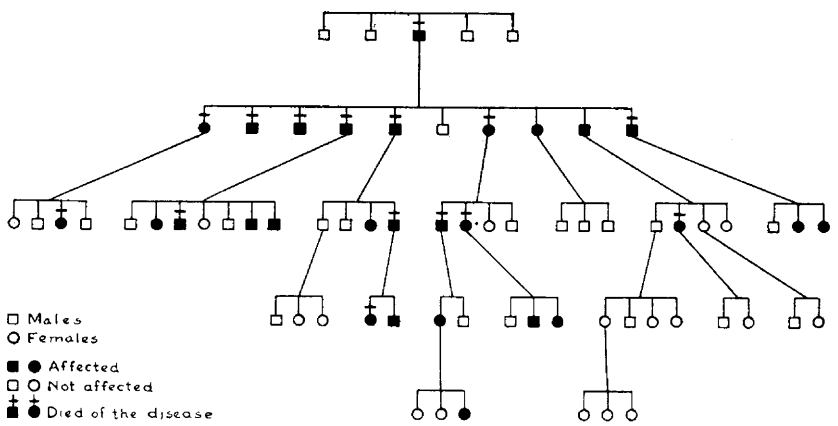
If we confine our attention to the children of affected parents only, it is found that 53 per cent. of them have inherited the parents' affliction. Confining it so, the details of the inheritance by generation and through the two sexes are shown in Table 2, in which the figures in parenthesis indicate the number of affected parents concerned.

From the figures in the last group in Table 2 it would seem that the inheritance is twice as likely to occur through the male as through the female line; but if we eliminate the children of the first affected father,

that is, the second generation, the difference is found to be rather less, though still striking. There is an instance in the literature, recorded by Cassirer,[22] in which the inheritance was entirely through the male line.

TABLE 2.—DETAILS OF INHERITANCE FROM AFFECTED PARENTS

Generation		Fathers	Mothers	Total
II	Total children of affected parents	10 [1]	....	10 [1]
	Affected children.....	9	....	9
	Per cent. of children affected....	90.0	....	90.0
III	Total children of affected parents	18 [4]	11 [3]	29 [7]
	Affected children.....	9	3	12
	Per cent. of children affected....	50.0	17.3	41.4
IV	Total children of affected parents	4 [2]	5 [2]	9 [4]
	Affected children.....	3	2	5
	Per cent. of children affected....	75.0	40.0	55.6
V	Total children of affected parents	....	3 [1]	3 [1]
	Affected children.....	....	1	1
	Per cent. of children affected....	....	33.3	33.3
Total	Total children of affected parents	32 [7]	19 [6]	51 [13]
	Affected children.....	21	6	27
	Per cent. of children affected....	65.6	31.6	53.0



Familial angioneurotic edema.

The known portion of the history of angioneurotic edema in this family is shown in the form of a chart, in which the children of each family group are shown (from left to right in the order of their birth), while those affected and those who are supposed to have died of the disease are indicated by distinctive markings. It is believed to be complete and correct for all the groups that are shown. A glance at the chart will show one striking fact: that the line of inheritance of the disease has always been direct. It does not skip and reappear, but continues in an unbroken line from parent to child. There are only two instances where all the children of an affected parent have entirely escaped the angioneurotic trait, and there is no instance of a child of

22. Cassirer: Lewandowsky's Handbuch der Neurologie, **5,** 256.

unaffected parents having exhibited the disease. This has not always been true of other angioneurotic families recorded in the literature; there have sometimes been skips and reappearance, but these are exceptions which are rarely noted; and direct descent is so constant as to suggest inheritance in the strict sense of a trait transmitted as a dominant characteristic under the mendelian law.

During many years the physical ills of all the members of this large family who resided in this community — and they include the majority of those shown in the chart — were looked after by Dr. J. R. Hinkle, a keen and able doctor of the old school, who, until his death some years ago at the age of 82, took great interest in their peculiar malady. After his death there were found among his effects some notes and letters concerning the family and their disease, from which many of the facts recorded in this history have been taken and which have added materially to its completeness.

Dr. Hinkle's experience with angioneurotic edema was unusual and extensive. It has probably come to few men to handle so large a group of related cases through so long a period of years; and his notes concerning it, while incomplete and often disconnected, are both interesting and instructive. His records bear no date, but were apparently prepared soon after 1890. While there is among them an entire absence of specific case histories or detailed clinical data, it is clear that he had studied his subject with much care, had gone thoroughly into the lineage of his cases, knew his patients well, and was conversant with the literature in existence at that time. The following quotations taken from his notes and letters give a better picture of the disease as it exists in the family under consideration than any that could be drawn from our own experience, and throw valuable side-lights on the clinical features of the disease. He says:

> For thirty years I have had four or five families to wrestle with who have all of these years been subject to such attacks. . . . We have them to the fourth generation. Throughout these generations, as far as they take the type of the C. family, they expect to have the disease; as far as they take the type of the father or mother outside of the C. family they expect to be exempt. This is largely true. . . . The family throughout are remarkably exempt from organic diseases. . . . They are not subject to morbid blushing.
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> The area involved may be from a small spot in the skin to the area of the back, . . . a single joint of a finger or toe, . . . on any part of the surface a spot not larger than a silver fifty cent piece. . . . A hand or foot will suddenly become doubled in size. Where the surface is larger and furnishes more tissue, as in the femoral region, the back, or sides of body, suddenly there will be a great roll apparently as large as a man's arm thrust under the skin, extending from pelvis to axilla, neck, or shoulder. Again it is circular in form—6, 8, 10, or 12 inches in diameter. . . . The swelling does not follow the course of muscles or other tissues.
>
> There is no part of the surface that I have not seen to suffer; also the tongue, larynx, lung, stomach, alimentary canal throughout. Every tissue except the bones and cerebrospinal axis may be involved. In one young lady, aged

18, the uterus in thirty minutes presented above the pelvis, as large and to the touch very much the appearance of a twenty-pound cannon ball. Pain was excruciating, not controlled by anodynes given heroically. In two and a half hours subsided, all quiet. . . . The heart is reported as having been involved. I have not seen such. An attack involving the heart would make short work of it. In such, death is immediate, hence a physician does not see them; nor is there any history except that they are dead. . . . In this community any statement as to the extent of the swollen condition of these people would not be classed as extravagant. To a stranger I do not know, hence I have not indulged in excess but have been moderate.

The swelling usually begins, or rather the first warning of the approach is in a small stinging sensation in the part attacked, described by the patient as the smallest possible point, but sharp and positive, probably the stretching of a single nerve capillary in the skin. Very soon this is multiplied and the tumor is perceptible. As the tumor increases in size the sharp pain does not increase in proportion to the increase of the tumor, but takes on a heavy feeling of compression, and motion in the part is obstructed. The skin becomes tense and shining, and distended often to the limit of its elasticity, the epidermis showing numerous checks and fractures. . . . There is no capillary engorgement, no throbbing pain, no wall of lymph as in an inflammatory process.

Vasomotor constriction is apparent in all attacks. In the outset it is the best guide to prognosis. If in the beginning of the attack the superficial circulation is fairly maintained and the artery is not too much constricted, there is reason to expect a favorable result; if the reverse, and there is a sudden receding of surface manifestation of circulation with the artery materially constricted, there may be little tissue involved as yet but there will soon be an unpleasant abundance, with collapse to the limit of life. . . . When any considerable amount of tissue is involved the depression is great. . . . The family has long since learned to look to this feature. If for a day or two a member is uncomfortable, manifesting a disappearing superficial circulation, the radial artery becomes narrow and constricted, there is great anxiety. If a swelling does occur at this time it will probably be extravagant. If the swelling appears suddenly and circulation is fairly maintained, the prognosis is favorable even though a large amount of tissue be involved if no vital organ be a victim. . . . The disturbed circulation may be manifest and no active swelling. We have clouds when we have rain; may have clouds and no rain.

In the young and others who are vigorous the swelling is usually very prompt in appearance; that is, in thirty minutes to an hour it will often be fully developed. Again it will be twenty-four hours in attaining its full force. The promptly developing attacks usually recede as promptly. With age or an exhausted system the swelling is much slower in developing, is not so intense, and continues longer, may be two or three days. As the vitality wanes the swelling moderates and finally ceases to appear, but the patient passes through all the other conditions of an attack, but it is not localized but diffused through the system. When this condition prevails, it requires a week or two to pass through an attack. Finally there becomes a continuous chronic morbid state that does not manifest remissions and exacerbations. The transition from the acute to chronic form is not sudden, but may be years. Nor is this a new neurosis or another variety, but the same disease with an altered and lowered vitality.

In your report you indicate that the attacks cease to occur in many, but even if not it does not kill. In the people suffering so here my observation is that they all die directly or indirectly of the disease, either in the acute stage when a vital organ is invaded or in the chronic stage. As they grow older, or in the young who suffer frequently, they cease to have the local tumefaction, but instead there comes a chronic degenerative neurosis (this is not the right name, but I do not know a better one) with lack of assimilation,

waste of tissue, muscles weakened, moving sluggishly. When they attain to this stage they drag out a miserable, tedious, semipainful, inert existence and die sure.

COMMENT

The clinical characteristics of the swellings in these cases as described in the above quotations correspond in the main with the descriptions given by our patient of his own attacks and of the many he has observed among his relatives. We believe there can be no doubt of their essential correctness, however extravagant they may seem. We may well doubt, however, the correctness of Dr. Hinkle's conclusion that the deaths from chronic degenerative processes among those who have been afflicted are still deaths from the same neurosis which at other times produces only acute and transient swellings. The application of modern clinical and laboratory methods would probably give a better explanation for many of these. But the history of the occurrence of many deaths in the acute stages of the disease, from the swelling of vital organs, and especially of the throat, is so clear as to be beyond serious question.

We have spoken of angioneurotic edema as a disease. This may be objected to by those who hold it only a syndrome. It is indeed a symptom only, like a convulsion; but it is, on the other hand, a fairly distinct clinical entity, not a part of any general condition which we are able to classify with perfect confidence, and for practical clinical purposes may best be called a disease.

The etiology and pathogenesis of angioneurotic edema are obscure. In the particular group of cases with which this paper deals, it is clear that heredity is the chief etiologic factor; but beyond that we are scarcely able to go. Obscurity begins at once in attempting to do so, for we are not aware of either just what is inherited or what determines its manifestation in the form of local swellings.

There have, nevertheless, been numerous attempts to explain the disease. By one, the causative rôle has been ascribed to alcohol; by another, to malaria; by others, to various intoxications and infections; each basing his conclusion on a particular observation which seemed to support his theory. Practically all observers believe that it bears a close relation to many nervous conditions, both functional and organic. It is not infrequently associated with migrain, with epilepsy, with chorea, with neurasthenia, and it has been observed to accompany the lightning pains of tabes. It is most commonly found in neuropathic persons, and is often so closely bound up with other symptoms of neurosis that it almost loses its identity. Families in which the hereditary form appears are usually neuropathic families.

No age or sex or social condition shows a special predisposition. While the disease develops most frequently in the third and fourth

decades, no age is exempt. It has been seen in early infancy and in those past the eightieth year. Of 210 cases collected by Cassirer,[22] 111 were males and 99 were females.

Sometimes the attacks repeat themselves with photographic correctness; sometimes they vary greatly. It has frequently been observed that one attack predisposes to others in the same locality — leaves some local sensitization which leads to future troubles. They may come once in a life-time, they may be repeated irregularly at intervals of years, or come on regularly or irregularly at intervals of months or weeks or days. And with all their repetition it may not be possible to find an exciting cause.

But it is sometimes otherwise. It has been frequently noted that small local traumas immediately precede the attacks. For instance, Halsted[23] saw an enormous swelling of the genitals develop immediately after a bicycle ride; and Courtades[24] saw the swelling develop after a blow in the eye of a boy aged 15 years, with recurrence thereafter in various parts of the body after any slight blow. Van Iterson[25] records a death from edema of the throat immediately following tonsillectomy, in which it was subsequently found that any small trauma was immediately followed by great local swelling. There are several cases like this in the literature. Three deaths in the family herein presented occurred from edema of the throat soon after the extraction of teeth. Thermic influences have often seemed to be the exciting cause, especially cold in many forms. Here probably belong those cases where the swelling comes only in the exposed parts of the body, as in the face and hands; and they constitute a large proportion of the whole number.

In other cases psychic influences seem to call forth the attack. The great emotions of fear and anger, or prolonged and arduous mental application have been observed immediately to precede the first attack. One of Cassirer's[4] patients always got the swelling when he first saw it appear in his child; and he refers to a patient of Steckel who always developed an acute edema of the leg when crossing a certain place unless he was accompanied by his physician, when the swelling did not occur.

But these facts, if indeed they are facts, scarcely clarify the subject. They do not explain the pathogenesis of the chief symptom, which is edema. It would seem that there must be some irritant to the capillaries concerned, and that through it either the lymph secretion is

23. Halsted: Am. Jour. Med. Sc., 1905, **128,** 863.

24. Courtades: Reference by Cassirer, Lewandowsky's Handbuch der Neurologie, **5,** 256.

25. Van Iterson: Reference by Cassirer, Lewandowsky's Handbuch der Neurologie, **5,** 256.

increased, or the vessel walls are so changed that they let through more transudate, or there is caused an increased absorptive power of the surrounding tissues. Experimental evidence of influence of this sort is not at hand, however, and we are left with only theories. Certain clinical observations, as urged by Cassirer and others, point strongly to the toxic, autotoxic, or infectious origin of certain cases. These come on acutely, recover, and do not recur except by repetition of the same toxemia. This group stands close to urticaria and purpura. On the other hand, the cases of direct or indirect heredity, in which the nervous conditions are predominant and which are related to other nervous affections, are apparently not dependent on outside influences. They regularly recur, and psychologic influences are etiologically important. But even here, it seems possible that through the influence of the nerves some toxic substance may be developed locally, causing temporary injury to the vessel walls or tissues; though wherein this supposed susceptibility of the nerves may lie is not known. In such cases we must deal with what appears to be an instability of the central nervous system, as in many other diseases, without positive knowledge of the nature of the defect.

A careful metabolic study of an angioneurotic woman, aged 54 years, was recently made by Miller and Pepper.[26] They found a slight increase of nitrogen retention during the attacks, and a reduced elimination of chlorids for three or four days preceding them, but no other changes. They believe that a low chlorid intake will have a beneficial effect on the attacks, but they do not find in their studies an adequate explanation of the cause. There is a tendency among some observers to find the glands of internal secretion at fault, but the relation is not made clear.

A point that seems not to have been considered sufficiently heretofore in this connection is that of specific or nonspecific protein sensitization after the manner of anaphylaxis. The history of idiosyncrasies in certain families, such as the tendency to hay fever and asthma, or the susceptibility to certain foods, has long been known. Similarly, a high degree of spontaneous sensitization to foreign proteins, specific or nonspecific in character and often multiple, with a distinct tendency for it to occur in families in which there is much evidence of inherited sensitization being transmitted as a dominant characteristic according to the mendelian law, has been recently pointed out by Longcope.[27] Herein may lie the explanation of angioneurotic edema. It offers the most fertile visible field for future investigation.

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26. Miller and Pepper: Metabolism Studies of Angioneurotic Edema, THE ARCHIVES INT. MED., 1916, **18,** 551.

27. Longcope: Am. Jour. Med. Sc., 1916, **152,** 625.

While the experimental study of immunity and anaphylaxis has seemed to establish the principle that transmission from mother to offspring, while it does occur, is in no sense a true inheritance, but is a passive transferrence of immune bodies to the child through the blood or milk of the mother and is very transient in character, Longcope has pointed out that the facts so far collected regarding the familial tendency of idiosyncrasy to foreign protein in man do not accord absolutely with those observed in experimental transference of immunity and anaphylaxis in animals. In the first place, sensitization in man is not transient, but often of years' duration; in the second place, it may continue through successive generations; and in the third place, it is often noticeable principally or solely in the male members. And finally, the sensitization may not always be to the same protein; in one family which Longcope studied the father was sensitive to horse serum and the son to egg-white. If inheritance is a factor, therefore, it cannot be simply by means of passive transfer from mother to offspring, but in some instances, at least, would seem to be a true inheritance of cell characteristics derived from one of the parents. In the important work recently published by Cooke and Vander Veer,[28] they have shown from a clinical study of the family history of 621 patients suffering from evidences of protein sensitization, chiefly hay-fever, that sensitization affects members of families in a proportion which closely approximates the theoretical figures of the mendelian law. They believe that the inheritance consists in the transmission of a tendency to sensitization only, or of a particular susceptibility, and not of the sensitizing substance itself. And they look on angioneurotic edema as a true anaphylactic reaction.

As to what may be the nature of the substances on which such a sensitization might depend in the case of angioneurotic edema we have no present knowledge, but it would seem that they necessarily must be common things and of general distribution, for in no other way can we account for the frequency and repetition of the attacks. Certain bacterial proteins might answer the requirements. It will be remembered that the original case of the disease in the family whose history has been presented was associated with an attack of quinsy. Is it possible that some sensitization to the products of the streptococcus could have arisen at that time which manifested itself later as a profound reaction to each mild flare-up of an infection which would ordinarily be harmless and pass unnoticed? And could the ubiquity of the streptococcus be responsible for keeping the sensitization active in particularly susceptible tissues? The suggestion is not made with confidence, but it may be worthy of consideration in future studies.

28. Cooke and Vander Veer: Jour. Immunol., 1916, **1**, 201.

A discussion of the symptoms, diagnosis, prognosis and treatment of angioneurotic edema lies beyond our present purpose. The symptoms are almost wholly occasioned by the swelling and will differ according to its location. If in the skin, the large, pale, elastic and nonpitting swellings, which are nearly free from abnormal sensation, should be readily recognized. The attacks come on acutely and are usually unheralded. They last for a few hours to a few days and disappear quickly, leaving no trace of their former existence. If the air passages are attacked, grave symptoms of obstruction may occur, leading even to death; but it is said that death is practically unknown except in the familial cases. If internal organs are invaded there may be much pain, and differential diagnosis becomes important. Not a few laparotomies have been performed in the belief that there was intestinal obstruction, as in the report of Bogart,[29] or ruptured tubal pregnancy, as in a case reported by Briggs.[30] The history of previous local swellings, either in the person concerned or in other members of his family, is important in this relation.

Concerning treatment, it only needs to be said that our efforts are rarely effective. Only to a small extent can we limit the attack, and we cannot prevent recurrence.

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29. Bogart: Ann. Surg., 1915, **61,** 324.

30. Briggs: Fulminating Pelvic-Abdominal Edema Simulating Ruptured Tubal Pregnancy, Jour. Am. Med. Assn., 1908, **50,** 528.