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T H E S I S for M. D. G R A D U A T I O N.

Entitled

A N G I O N E U R O T I C O E D E M A.

A Contribution to its Historical and Clinical Study, with special Reference to Cases recorded as occurring in Families.

Presented by

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I N T R O D U C T O R Y.

It stands to the credit of the professional acumen of this country that the first clear description of a case exhibiting the group of symptoms, later to be known by the title of this paper, was given by that master clinician, Graves,[27] of Dublin, in 1848.

A second case was in 1872 presented at a meeting of the London Medico-Chirurgical Society by Milton, and it was considered a rare variety of disease, only one member present having seen a case at all like it. Milton gave wider publicity to this case, and several others, which were, however, complicated with Urticaria, in a paper, entitled "Giant Urticaria" in the Edinburgh Med. Journal, Dec. 1876.[47]

In the space of thirty years that intervenes between then and the present day, much close study has been devoted to this malady, and a voluminous literature, recording well over 200 cases has grown up in connection with it. Its interesting history shows that it soon stepped beyond the special domain of dermatological study, and at the present day it stands in near and important relationship to the work of the general physician, and ~~to the~~ surgeon, as wwell as to that of the specialists in Ophthalmology and Laryngology, and most of

all to that of the Neurologist and the student of Heredity. Notwithstanding all this, the importance of Angioneurotic Oedema is not at all fully recognised by the medical profession generally. It is still too commonly looked upon as a trivial ailment, like Urticaria, occurring in neurotic persons.

I propose in this Thesis, by a review of its history, by the presentation of cases of my own observation, and, more especially, by the record and analysis of cases reported as occurring in families, to show that where there is an inherited predisposition Angioneurotic Oedema is indeed a most serious malady, and that even in other cases it is capable of producing a much greater amount of bodily discomfort and mental distress than is commonly supposed.

DEFINITION.

No better definition of Angioneurotic Oedema can be given than the classical description of Quincke, its first great investigator on the Continent, published in the Monatshefte fur prakt. Dermat., July, 1882, p. 130, under the title of Acute Circumscribed Cutaneous Oedema.--

Oedematous swellings, with a diameter of from 2-10 cm., make their appearance in localised places in the skin and subcutaneous tissue, most frequently affecting the extremities, especially in the neighbourhood of the joints, but the face and trunk are also involved. The normal colour of the skin is not essentially altered, at times it may be either paler or redder than normal. There is some tension and itching. The mucous membranes can also be affected, the lips, the uvula, the pharynx, the larynx, and the mucous membrane of the stomach and intestines. The swellings come and go rapidly, in the course of hours, or, at the most days, but they recur frequently. The general condition is, as a rule, not affected. The malady has close relations, and shows trasition forms between itself and Urticaria.

To this description of "Quincke's Oedema" a synonym for the malady still often in use by continental writers, later years have found little to add. It may, however be pointed out that the face is found to be the most common seat for the affection; and also that those affected but very rarely complain of a sense of itching associated with the oedema.

H I S T O R Y.

In 1882, Dinkelacker,[17] a pupil of Quincke, published a dissertation upon the cases of Quincke with an account of hitherto recorded cases.

In 1883 Jamieson[35] described in the Edinburgh Med. Journ. an interesting case, associated with Rheumatoid Arthritis.

In 1885 Strübing[87] first definitely labelled this condition with the title of Angioneurotic Oedema, which seems the now generally adopted designation, though at first it had to fight its way through a host of rival synonyms. The cases of Strubing were among the earliest of the family group, and all illustrated the distressing gastro-intestinal disturbances that are so marked a feature of these family cases.

In 1886 Rapin,[64] whose contributions are the most important early ones in French literature, discussed the question under the title of "DE quelques formes rares d'Urticaire" It may be remarked here that, until comparatively recent years, French writers have mostly regarded this malady solely as a division of Urticaria. They have often, too, with, apparently, little justification, referred to this malady under the term "Oedemes rhumatismales."

IN 1887 Matas[44] observed a case associated with Malaria.

In 1888[55] Osler greatly furthered the study of the subject by publishing his remarkable series of 22 cases occurring in one family, throughout five generations.

Börner[7] also published a useful treatise on the occurrence of oedemas in connection with menstruation, pregnancy, the puerperium, and the climateric period.

Riehl[66] also recorded several cases, one exhibit-

ing the effect of strong mental shock in bringing on the characteristic oedema.

In 1890[36] Joseph narrated three cases of his own, one associated in a remarkable way with Urticaria, in which the two eruptions, even when out at the same time seemed to retain their respective characters. Another case was complicated with Haemoglobinuria, and the third showed the relation of the oedema to alcohol.

In 1891 Courtois-Suffit[13] gave a careful review of the subject from the standpoint of French medicine.

In 1892 Collins[11] most ably reviewed the published cases, contributing also a few of his own. To this American investigator all subsequent students are indebted for the valuable statistics relating to no less than 72 cases.

Starr[72] contributed several cases, one showing cleary the influence of cold in producing the oedema.

Jacob[34] brought out in several cases the tendancy to suffocative attacks in this ~~connection~~ condition.

In 1893 Bauke[6] laid emphasis upon the nervous elements in the malady.

In 1896 Yarian[85] recorded another family series

Mettler[46] reported a fatal case from Oedema of the Glottis.

In 1898 Schlessinger,[67] one of the most valuable of Germany's contributors to our knowledge of this disease, published an interesting account of a family group.

In 1899 Schlessinger[68] took a wider survey, and, with much sound reasoning, urged that certain forms of Asthma, and intermittent swellings of joints and tendon sheaths should be added to the oedemas of skin and mucous membranes, and as a new designation to embrace all these he suggested the term Hydrops Hypostrophos.

In 1900[57] Osler published the first of an interesting series of papers on the "Visceral relations of the Erythema Group," pointing out that gastro-intestinal disturbances were not uncommon in connection with

the various forms of Erythema, Purpura, Urticaria, and Angioneurotic Oedema, and urging that on this basis they should be grouped into a class by themselves. It may be remarked, in passing, that the cases collected by Osler were mostly of a much more serious character regarding the general health than is met with in Angioneurotic Oedema, a considerable proportion dying of renal disease, a condition, which, he admits, he has never found in uncomplicated Angioneurotic Oedema.

Cassirer (9) published his masterly monograph on the Vaso-motor and Trophic Neuroses. A lengthy section of the book is devoted to the discussion of Angioneurotic Oedema. The exhaustive bibliography attached is most invaluable to any student of the subject.

In 1902 Griffith (28) made the first valuable contribution from England to the steadily accumulating material for the study of family cases, reporting the death of a father and a daughter from Oedema of the Glottis.

Mendel (88) gave the history of another in which out of twelve members six had succumbed to it out of a family of twelve

In 1904 Ensor, (22) in Guy's Hospital Reports, published what is perhaps the most valuable account of the occurrence of this disease in families. He gives the record of thirty cases of the disease in a family of eighty members, and of this number no less than eleven have died of suddenly developed asphyxia.

Morris (49) made an extremely important addition to the knowledge of this subject. While lavage was being perfomed to relieve the symptoms of a gastric crisis, a piece of mucous membrane was detached from the wall and was brought up by the stomach-tube. Microscopic examination showed that it was oedematous, and a careful study of it leads to the conclusion that it confirms the idea, long entertained, that the gastric symtoms are produced by an oedema analagous to that of the skin.

Morris (50) reports the death of this patient the following year from oedema of the glottis, and his paper

is accompanied by photographs which clearly illustrate its deep-seated location.

In 1905 (31) Harrington, while operating upon a patient, who was subject to Angioneurotic Oedema, when an intestinal attack was on, found a definite oedematous swelling, in the wall of the bowel, not far from the Appendix. This fact may be taken as a demonstration that the colick and vomiting so often associated with these cases are due to disturbance of peristalsis through the presence of these swellings in the bowel

Ouvray, (59) in a These de Paris, recorded a valuable collection of cases of the family series.

In 1906 Diller (16) in connection with some of his own cases, appends a useful bibliography of recent literature.

In 1904, Quincke (66) the veteran investigator of this malady published an important paper, in association with Gross, upon the more uncommon localisations of the oedema, and I do not think that I can more appropriately end this historical survey than with the following quotation of his words.--

"One is perhaps justified in thinking that the transient rheumatic pains (as in Lumbago) and many Neuralgias, also Migraine, many of the phenomena of Hysteria, and many disturbances of central origin, exhibiting themselves in the motor or psychical field of action, may arise in a similar way, namely through sudden oedematous effusions."

CASE, No. I.

Own Observation.

J. E., aged 69 years at the present time, is a retail druggist, residing at Auckland, New Zealand. He has taken an active and prominent part in the business affairs of the city, and, though of a decidedly high-strung "nervous" temperament, he has on the whole enjoyed good general health.

Six years ago, while on a visit to Sydney, New South Wales, one Sunday morning, as he was proceeding to church, about two hours after breakfast, he perceived an irritation in the mucous membrane of the lips and the front of the gums of each jaw, and almost immediately he became conscious that his lips and face were beginning to swell. He thought that he must have been stung by some insect. By the time he returned to his hotel for lunch, the swelling of both lips and both sides of his face was quite pronounced, and continued steadily to increase until it seemed to reach its height shortly before his bedtime. The parts affected had a firm hard feel, but were not painful to touch, and the skin was not reddened. He took his temperature and found it normal, and apart from the uncomfortable feeling of tension he felt quite well. He had no nausea or other indication of gastric distur-

bance. He bathed his face freely with hot water, and took a saline purgative and when he awakened in the morning, the swelling had almost entirely disappeared. In seeking for a cause of this attack, he was inclined to put the blame upon some smoked fish which he had taken for breakfast on the Sunday morning.

A few months afterwards, having meanwhile returned to New Zealand, he had a similar attack, which came on during the night and was well developed when he awoke at his usual hour. On this occasion he was unaware of any dietetic or any other cause.

During the succeeding five years he has had at irregular intervals of from three to six months no less than a dozen attacks of distinct severity, besides a number of minor ones of which he has not kept count. They almost invariably came on in the early hours of the morning during sleep, and on awaking at his usual hour, between 6 and 7 a.m., he would find his lips and face considerably swollen. At times the swelling developed with great rapidity, and he describes being awakened at 2 a.m. one morning with such a sense of immobility in one side of his face that he feared that he had been paralysed but on getting a light and looking in a mirror he saw that it was his "old trouble." The swellings take from about twelve to eighteen hours to reach their maximum, at which they are maintained for about the same length of time, after which they begin rapidly to disappear, and are quite gone

by the end of the second, or, at most, the third day. Both the lips and both sides of the face are affected in the severer attacks, but in the milder ones only the upper lip and only one side of the face.

He has watched his diet with the utmost care, and he came to the conclusion that "fish" smoked or fresh was not to be held responsible for attacks subsequent to the first. He recollected that on one occasion he had an attack after having had some tinned pears for his evening meal, thogh previously and since he has eaten tinned fruit with impunity. Exposure to heat or cold seems to have no provocative effect, and the season of the year makes no difference. He is inclined to believe that he is more prone to an attack after he has been exposed to over-fatigue through too much physical exertion.

HE has never had any rise of temperature or other "feverish" symptom, and, apart from the very uncomfortable feeling of fulness and tension of the parts affected, which, by the way, never "itch" his general health seems to be but little, if at all, disturbed. Whilst not conscious of any gastric derangement before or during an attack, he has often noticed that his digestion does not seem quite right for a day or two afterwards.

I was called in to see him professionally in September, 1905, when he gave me the account of his malady which I have just recorded. His face was greatly

disfigured by a large oedematous swelling involving both lips and extending up the cheeks, on the right side as far as the lower margin of the lower eyelid but not quite so high on the left. The upper lip must have been almost twice its normal size, projecting rigidly and nearly immobile; the lower lip was also considerably swollen, and he required frequently to make use of his handkerchief to restrain the saliva from overflowing from his imperfectly closed mouth. He had awakened between 2 and 3 a.m. with the peculiar irritation of the mucous membrane of the lips and the gums which had so often ushered in an attack, and by 7 a.m., when he got up, the oedema was very marked and it had steadily increased in volume until the time of my visit, 3 p.m. The lips and cheeks had a firm elastic feel, and did not give the slightest indication of "pitting," on pressure. The colour of the skin was unaltered over the oedematous patches, and the mucous surfaces of the lips and gums appeared likewise normal, and a careful examination of the mouth revealed no sign of inflammation, or of any local cause of irritation. The swollen parts were not at all tender or painful when handled. The affected parts were very uncomfortable to the patient on account of their great tension, but he had no feeling of burning or itching in them. Apart from the annoyance caused by being detained within doors by this disfiguring oedema, he felt in his usual state of good health.

A careful physical examination showed that his heart, lungs, and the digestive system were in a thoroughly healthy condition, and the urine, of which several specimens were taken, was free from albumen, casts, sugar, or other abnormality. His bodily temperature and rate of respiration were normal. He was, as mentioned above, a man of a marked nervous temperament, and for many years he had found it necessary to retire early to rest and avoid all excitement in the later hours of the day, otherwise he would suffer from distressing headache and insomnia. Except for occasional attacks of indigestion, he has had general good health throughout his life. He had, however, between the age of forty-five and fifty a large number of peculiar attacks of colic, affecting apparently the descending colon, which came on without any definite connection with food, and which after lasting several hours disappeared as suddenly as they had come on.

He is a non-smoker, and is very abstemious in the use of alcohol.

No history could be obtained of the occurrence of any attacks of angioneurotic oedema or urticaria in his ancestry or in his children, of whom he has two sons and three daughters living. One son died at the age of twenty-five from what was diagnosed as tubercular meningitis, though I understand there was considerable doubt as to the nature of the case.

The patient continued the treatment to which

he had been accustomed of alkaline draughts and purgatives, and by next morning the oedema had largely subsided, but it was not completely away until early on the morning of the third day.

I had not another opportunity of seeing this patient during any subsequent attack, but in a letter dated, Dec. 21st. 1906, he says "The last attack, about a year ago, took quite a new phase--this time I was seized with a sudden and alarming swelling of the left eye, the effect of which passed off in a day or two".

CASE, No. II.

(Own observation, supplemented by notes placed at my disposal through the kindness of Dr. A. J. Whiting, Assistant Physician, Tottenham Hospital, North London.)

On October, 21st.,1906, while attending the Post-graduate Course of Study connected with the Tottenham Hospital, North London, I first saw the patient and obtained from him the following history.

G. C., aged, 70 years, residing in Tottenham, a collector for an insurance company by occupation, had always enjoyed exceptionally good health up to April, 1903, at which time his wife died suddenly from an attack of apoplexy while away from home on a visit to her son. This bereavement caused a great shock to his nervous system, and he was much "run-down" in health for a long time afterwards. Sometime in November, 1904, he noticed, on awaking from his sleep, early one morning, about 4 a.m., a small hard lump on one side of the tip of his tongue, and this lump continued rapidly to enlarge and spread until it, in a few hours occupied the whole of the half of the tongue on that side. SO much swollen was the tongue that he could speak only with great effort, and found considerable difficulty in swallowing. He was much alarmed, but was relieved to find that in the course of a few hours the swelling began to show signs of diminishing, and it had almost

completely vanished by noon, although a feeling of awkwardness in moving the tongue remained throughout the day. Beyond the discomfort of its increased bulk, there was no sense of pain or irritation in the tongue. After the lapse of a fortnight or three weeks, a similar attack occurred. He then consulted a medical man and was placed under a long course of treatment for indigestion as the doctor thought that the cause of his trouble must be due to some digestive disorder. In spite, however, of treatment, extending over many months, the swelling of the tongue recurred at fortnightly or three weekly intervals, always affecting one half, right or left, with about equal frequency. In August, 1905, he had another great psychical shock through the loss of a daughter, who was killed by a stroke of lightning at her home in Canada. After he had news of this sad event, he noticed that his attacks became much more frequent, coming every few days or at not more than a week's interval. He also observed that in addition to the affection of his tongue, a similar hard lump would make its appearance at one side or other of his upper or lower lip, and it would increase rapidly until it had reached the size of a large filbert nut. Large swellings would also occur in the mucous membrane of the right or left cheek. Sometimes the three places on one side would be swollen at the same time. Then, again, when the swelling had disappeared at one place it would begin at another.

Almost every attack is preceded by a peculiar sensation of dryness in the mouth, which he describes as a "metallic" taste, and when he awakes with it in the early morning he knows that the swelling will invariably follow within an hour or two. On rare occasions he has had this oral dryness for twenty-four hours before an attack. The attacks, almost without exception come on between 4 and 5 a.m. He feels so uncomfortable with the dryness of the mouth and the rapid swelling of his tongue that he cannot lie still, but must rise from his bed and walk about the room, all the while moving his tongue to try and excite the secretion of saliva, and sipping fluids to endeavour to relieve the dryness of the mouth. He says, however, that nothing he does ever seems to cut short an attack, and it steadily advances to its height, and after remaining there for an hour or two it then rapidly diminishes and is usually quite away before the middle of the day. As his condition was not improving his medical adviser sent him as an outpatient to the Tottenham Hospital to consult Dr. Whiting, whom he first saw on October, 2nd., 1905. Under the treatment received his attacks became less frequent, recurring at intervals of a fortnight or three weeks, and during the last six months the swellings had also not been so large, as a rule, and he had not been so much troubled with the dryness of the mouth.

He has always carefully watched his diet, and had never been able to trace an attack to any special

article of food. He is moderate in the use of alcohol and tobacco.

On the morning of the day on which I first saw him he had awakened at 4 a.m. with the "metallic" taste in his mouth and the swelling in his tongue. The attack had been one of only moderate severity, and when I examined him at 11 a.m. there was a distinct swelling involving the whole left side of the tongue. This side of the tongue had a hard resistant feel, and was not painful to pressure. There was no perceptible difference in the colour of the two sides of the tongue.

The patient presented the appearance of a perfectly healthy man, remarkably active both physically and mentally for his time of life. He did not give any indication of being of a neurotic or highly strung nervous temperament. An examination of his cardiac, respiratory, digestive, and other systems showed them to be in a perfectly healthy state, and his urine contained no albumen, sugar, or other abnormal constituent. The temperature and pulse were normal.

The hospital records, and the personal assurances of Dr. Whiting bore out these observations as to the absence of the "nervous" temperament, and as to the general soundness of his health during his long and constant attendance at the hospital, and they also confirmed the patient's statements regarding the localisation of the oedema.

He was at first treated with Tabl. Trinitrini, 1--100th. of a grain, for some weeks without any improvement. Since last April he has been taking Thyrroid Tablets, 2½ grains daily at bedtime, and he considered that they have benefitted him greatly for the attacks have not been so severe and he has not been nearly so much troubled with the distressing dryness of the mouth.

I last saw the patient on February, 12th., 1907, when he reported that he had not had an attack for nine weeks, the longest spell of freedom he had known since his malady had begun.

CASE No. III.

(The hitherto unpublished notes, with a photograph of the patient, kindly placed at my disposal by Dr. A. J. Whiting, Assistant Physician to the Tottenham Hospital, North London.)

C. M., aged, 19 years, domestic servant, was admitted on December, 8th, 1903.

Father and mother well. Patient has six younger sisters, all well and healthy, one brother died of consumption. No history of similar conditions in the family, nor of Rheumatism. Patient had Whooping Cough when four years old. She had an attack of Measles not long before the onset of the present trouble. The rash was very marked especially over eyelids and she could not see. She is also supposed to have had an attack of Measles in her childhood. She began to menstruate at fourteen, and has always been regular.

Her present illness commenced nearly seven years ago. Her right arm began to swell, very quickly, and although she had a loose sleeve on it was necessary to slit it up at once to give her relief. The next morning the left eye was swollen and watering. Since then she has had attacks every three or four weeks, the swelling varying in position and size, sometimes only one side of face being affected, sometimes both. The ears, lips, nose, cheeks, eyes, throat,

are all affected at times, sometimes several together. Occasionally she has a little colic, but never any sickness, vomiting, or haematuria. The patches of skin affected vary considerably both in shape and extent, depending on the situation. There is no abrupt line of demarcation, but each swelling is distinctly localised. The swellings do not pit on pressure. There is marked Dermatographia present all over the body. Before the attack is coming on, she feels a sharp tingling, or burning, sensation passing over the part that is going to be affected.

She says that heat or cold or the change of the seasons makes little , if any , difference, although she thinks that cold is more likely to cause an outbreak than heat. She says she is nervous and easily excited, but exertion and excitement do not seem to influence the attacks. She has no annoying mental sensations during the attacks. The upper lip always swells more than the lower one. Sometimes the condition affects the tongue which feels too big for the mouth and protrudes a little. Sometimes, too, she feels a swelling in her throat,which causes some difficulty in swallowing and breathing. The legs and arms, separately, or together become affected, also the vulva gets swollen at times. The swelling also appears on the soles of the feet and between fingers and toes

State on Admission.--Temperature, normal. Pulse, 88, Respiration, 20. She looks well and healthy, with a bright, lively, temperament. Face has a good colour. Appetite and digestion good. The Spleen is somewhat enlarged, and can be palpated on deep inspiration. There are no enlarged glands. The blood, on microscopic examination, showed a slight increase of leucocytes. The Circulatory, Respiratory, Digestive and other Systems appeared quite normal. There was no trace of Albumen in the Urine.

Dec, 10th. Tongue slightly swollen.

Dec., 12th., Last night and this morning, the right eye was swollen and painful. At 6.30 p.m., the left ear became affected.

Dec., 13th. The right hand, especially on the thenar and hypothenar eminences, was swollen, painful and moist.

Dec. 14th. The throat was swollen during the night on the right side, but cleared up this morning. The right hand is still oedematous and painful.

Dec., 15th. Redness and swelling on the thentr eminence and along the inner side of the right arm, following more the course of the lymphatics, but situated more in patches of redness and swelling, firm and hot to touch. The swellimgs were most tender over the Biceps muscle.

The attack gradually subsided, and the patient left the Hospital on Dec., 19th.

She removed from the district shortly after this date and no further record of her history has been obtainable.

The treatment chiefly adopted in her case was a mixture containing Calcium Chloride, grs., 10, three times daily, after meals. IT was, however, without any manifest effect.

The attatched photograph was taken during an attack, chiefly involving the lips, which came on during the five or six weeks when she was attending as an outpatient before admission into the Hospital. The picture of the facial disfigurement which this malady is capable of causing is most clearly exhibited in this photograph.

C O M M E N T A R Y.

CASE, No. I.

Age.--It is very rare for Angioneurotic Oedema for the first time to occur over the age of sixty. Case No. II is, however, another instance, and other cases are reported by Baruch,[6] Herter,[33] and Raven.[65]

Temperament.--The fact that the patient was of a highly-strung nervous temperament, yet in no sense neurotic or hysterical, is of fundamental importance in forming a clear clinical conception of the malady under consideration. A great need in medical literature is some simple term which would denote the peculiarly easy excitability of the Nervous System in the subjects of Angioneurotic Oedema, yet which is lacking these physical stigmata and Psychical abnormalities that attach themselves to the true Hysterical and Neurotic conditions. Though such a temperament is by no means indispensable to form the groundwork for the development of the disease yet it is noted as being present in the majority of cases.

Diet.--The apparent close connection of the first attack with the eating of "smoked fish" is very noteworthy, for it suggests, at first sight, the possibility of ptomaine poisoning or of Urticaria.

The very rapid development of the oedema, the absence of marked gastro-intestinal symptoms, and also of fever are against the idea of ptomaine poisoning, and much more in favour of Urticaria. There was, however, no sign of the typical "wheal" formation, nor any of the characteristic redness, associated with intolerable itching, of Urticaria. It is to be remembered, however, that there is a close alliance between Angioneurotic Oedema and Urticaria as has often been pointed out by Quingke,(62) Joseph,(36) Rapin,(64) Osler,(56) and others. Whilst in most reported cases of Urticaria, it is observed that an outbreak will almost invariaby be associated with the taking of some particular article of diet, and will inevitably occur if that food is taken, yet in the records of some two hundred ~~cases of~~ published cases of Angioneurotic Oedema, that I have examined, in perhaps not more than a dozen could any article of diet be specified as the cause of an attack, and even in some of these cases it was noted that an attack did not invariably follow; and such was the case in this patient of mine.

Disturbance of Digestion.--Complaints of a disordered condition of the digestive system are of frequent occurrence in connection with this malady. The fact that this patient some years before suffered from severe attacks of colic is deserving of note. I regret that at the time I saw him, I was unaware of the close

association, which the researches of Osler had demonstrated, between intestinal colic and cutaneous oedema, else I would have obtained fuller particulars as to the details of their occurrence. Quincke,[63] in a paper published in 1904, has emphasised the fact that paroxysmal attacks of intestinal disturbance may for many years precede the appearance of the oedematous affection of the skin or visible mucous membranes in many patients.

Heredity.--I have alluded in the history of the case to the fact that one son of the patient had died from what had been diagnosed as Tubercular Meningitis, but about the accuracy of which diagnosis there was, I understood, some doubt. The symptoms, I gathered, came on rather rapidly and violent headaches formed the most prominent feature. The fact that Osler[56] and other observers have expressed the belief that brain symptoms may develope on an Angioneurotic basis has lead me to comment on this point in my patient's family history, though the meagre details give me no justification to make any further use of it.

Localisation of the Oedema.--The lips, eye-lids, cheeks, and forehead share the honour of being the "Sites of election" for Angioneurotic Oedema, and in many cases they are the only areas of the body that are affected. Curtis[15] states that he has seen from 12-15 cases in which one or both lips were the only parts affected, and says that in nearly every instance the oedema came on at night and the patients

were first conscious of it on awaking in the morning.

The freedom from any trouble in the lips for nearly a year and then the oedema beginning anew in a fresh place, namely, the eye-lids is a phenomena of not uncommon occurrence. The following case reported by Riehl[66] illustrates this clinical feature in the reverse order.---

> A school teacher, aged 38, who had enjoyed general good health, and had a good family history in regard to skin and nerve diseases, had the misfortune to be bereaved of his wife, and a few days afterwards, he first noticed a swelling of the lids of the left eye. The swelling came on through the night, and by the morning he was unable to open the eye. In twenty-four hours he was all right again, and there was no disturbance of his general health. For the next three or four years at intervals of three or four weeks the left eye was exclusively affected. In the year 1878, four years after his trouble began, the right eye was similarly affected, and the oedema would at the same interval of three or four weeks attack the right or left one alternately or both together. In later years, at the same time, or independently, the oedema made its appearance in his lips, which would project like snouts (russelartig), and also in his right cheek. The attacks mostly came on at night,

reached their height by morning, and he was, as a rule, able to go to his work by noon. In the year, 1885, he had, one night, oedema of the Larynx and Pharynx, with difficulty in breathing and swallowing, but the symptoms had passed away before the morning.

CASE No. II

Absence of the "Nervous" Temperament.--In a large minority of cases of Angioneurotic Oedema the patients are reported as being in good general health and of perfectly sound constitution in regard to the Nervous System. In some such cases the stability of the Nervous System has been upset through some sudden mental shock or severe emotional strain as in this case and in that of Riehl just quoted. Starr[72] also mentions an attack in a mother after the loss of three children at one time.

Localisation.--Cases in which the oedema is principally confined to the tongue are published by Joseph[36], Herter,[33] Raven,[65] and Baruch[5] amongst others, although the unilateral character of the swelling is not always so clearly marked as in this case of mine. Baruch's case presents several points of similarity, and I consider it useful to quote it at some length.-

> The patient, a lawyer by profession, was aged 60 years, when he first noticed that at certain times his tongue became swollen so that it seemed to entirely fill his mouth, making it extremely difficult to speak, and embarrassing

his breathing, and at the same time he felt a tense and painful feeling in his throat. These attacks always came on at nights, usually after a sound sleep, from which they would arouse him in the early morning hours. The tongue remains swollen from two to three hours, and when improvement commences the swelling disappears in from ten to twenty minutes. The attacks are always accompanied by great mental and physical depression and fear of impending death, and he remains depressed for several days. At first the attacks were every two or three months; but now every week or fortnight. His urine was normal. He had no gastric or intestinal symptoms. No cause could be assigned for the out-breaks. He had no cutaneous lesions.

The mental distsess and apprehension observed in this case of Baruch's is of considerable interest. I enquired carefully in my case as to the reason for my patient always getting up when an attack came on; but although his only reply was that it "made him fidgetty" to lie still and he thought it did him good to walk about, yet he conveyed to me the impression that he had the fear of impending death through suffocation. Mendel (83) also points out how repeated attacks of oedema of the tongue and throat may lead to the establishment of mental depression.

Time of Occurrence.--The early hours of the morning, between 2 and 4 a.m., seem undoubtedly the the most favourable time in the day for the onset of the attacks of Angioneurotic Oedema. This fact is very clearly established by this present case, and by No. I and the cases already quoted from the observations of Curtis,[15] Riehl,[66] Baruch,[5] Herter,[33] and might be supplemented by many other references. The question naturally arises as to what relation such a remarkable fact has to the pathology of the malady. In discussing the question it would be advisable to first refer to the latest views of Physiologists in regard to the part played by the vaso-motor centre in the causation of sleep, and I will quote some references from Professor G. N. Stewart's Manual of Physiology, 5th. Edition, 1906.---page, 768.--

> "The tone of the vaso-motor centre is diminished and the arterial pressure falls during sleep. But a fall of general arterial pressure is usually accompanied by a diminution of the quantity of blood passing through the brain. So that the balance of evidence is decidedly in favour of the view that sleep is associated with a certain degree of cerebral anaemia. As to the nature of the relation between the two conditions, it has been suggested that the anaemia is produced by

> fatigue of the vaso-motor centre, which causes it to relax its grip upon the peripheral blood-vessels, and that the condition of the cortical nerve-cells, which we call sleep, is directly produced by the lack of blood. But there does not appear to be any good reason for believing that the vaso-motor centre is more susceptible of fatigue than the higher cerebral centres. On the contrary it is probable that the bulbar centres are less delicately organized than the higher centres. In any case, if the cerebral nerve cells 'go to sleep' because their blood-supply is diminished, ought we not to look for a similar cause for diminished activity of the vaso-motor centre ?"

It would therefor appear that in this period of 'sleep,' or diminished activity, the vaso-motor centre would be most liable to have its stability interfered with in the way shown by the phenomena of Angioneurotic Oedema. It appears most probable that this malady is due to an inherent or acquired defect in metabolism, and some constituent of the food, not normally dealt with in the process of digestion, entering the circulation in the early hours of the morning, disturbs the vaso-motor system when it is most open to attack.

Interval between attacks.--The consistent regularity with which the attacks recurred at intervals of two or three weeks over a long period of years as illustrated in this and the other cases quoted is one of the striking features of Angioneurotic Oedema. Collins [11] reckoned an average interval of 19 days. I find an average of 27 days in the recorded cases accessible to me; but with such various intervals in different individuals it is impossible to form anything but an approximate estimate. It would be safe, however, to say that individuals affected with this disease rarely go from three to four weeks without an attack.

Premonitory Symptoms.--The metallic taste, or excessive dryness of the mouth, which ushered in an attack, is most noteworthy, and is, as far as I can gather, a most unique experience. In Herter's case [33], in which a woman, aged 61, was troubled chiefly with oedema of the tongue, there was not only an excess of oral secretion but of nasal as well. An increase in secretion from the mouth seems certainly the rule in cases of oedema of the tongue and lips. The peculiar 'aura' in this case would certainly point to a definite involvement of the secretory as well as the vasomotor apparatus, and its further investigation may furnish some interesting information about the process whereby the succeeding oedema is brought about.

Treatment.--The somewhat beneficial effect of small doses of Thyroid extract, continued over a long period, is worthy of note, as the therapeutic resources in dealing with Angioneurotic Oedema have so far proved to be very limited.

CASE No. III.

Sex.--The much greater readiness with which females as a rule become the subjects of disorders of the Nervous System would lead one to suppose that they would furnish by far the larger proportion of subjects of Angioneurotic Oedema. Such, however, is not the case, and a study of the records brings out the surprising fact that the number of males greatly preponderates. Collins found in 75 cases twice as many males as females. Cassirer in 163 cases found a much less marked difference, namely, 70 males and 63 females. I have searched the records of 95 cases published since 1900, the date when Cassirer's book was issued, and my figures practically coincide with those of Collins, 64 males and 31 females.

Age.--This patient approaches more nearly the usual age for the out-break of this malady than my other two cases. A reference may again be made to the statistics of Collins.(11) He estimates an average for the age at time of first attack at 27 years. Cassirer finds an average of 25.8 years. I have

perused the records of 205 cases, and find an average of 21 years. The gradual lowering of the average age is due to the increasing number of cases occurring in families, in which class of case the disease often first shows itself in childhood, or at any rate before puberty.

Localisation.--The distribution of the oedema is in this case much more general than in the other two. Affection of the extremities come next in frequency to that of the face. They all are the parts of the body most exposed to changes of heat and cold, and to slight traumatisms. I do not remember meeting with any previous reference to affection with oedema of the vulva except in a case reported by Mendel.[88] In the male the involvment of scrotum and penis is several times alluded to, by Collins,[11] Morris,[49] Atkins,[1] and others.

Acute Development of the Oedema.--This rapid development of the oedema is one of the most essential features in the malady. The necessity for almost at once having to slit up the loose-fitting sleeve of the patient's jacket illustrates this point well. The remarkable suddenness of onset often gives rise to the impression that the patient has been stung by an insect, (Case No.I), by a spider, (Rapin[64]), by a wasp (Curtis[15]).

Unusual Symptoms.--The red appearance of the skin involved in the oedematous swelling is not unfrequently reported, but most commonly the skin retains its normal appearance. The pain or tenderness complained of by the patient at the seat of the oedema is a very exceptional symptom. In regard to the feeling of heat in the swelling recorded cases give little material for comparison, and in only one case, that of Starr's,(92) do actual thermometric measurements seem to have been taken. Secretory disturbances as indicated in this case by moisture of the swollen hand is of the utmost rarity, and Börner(7) alone mentions a case, in which the hand was also affected.

Measles.--If one accepts the reported occurrence of Measles in childhood, I should think that it is very likely that the so-called second attack was in reality an Angioneurotic Oedema, involving the eyelids and forehead.

Dermatographism.--This indication of vasomotor instability so prominent in this patient is very rarely alluded to in the literature of Angioneurotic Oedema. Its occurrence in a case reported by Cassirer(9) is the only instance that I can recall.

E T I O L O G Y.

With abstract and analysis of the published Cases occurring in Families, showing the importance of Heredity.

In the foregoing pages reference has been made to the etiological significance of Sex, Age, Occupation, Heat and Cold, slight Traumatisms, and above all a peculiar Excitability of the Nervous System, and I propose now to devote some consideration to the remarkable tendancy for Angioneurotic Oedema to occur in families, thereby enforcing the conviction that in this singular malady, the preponderating etiological factor must be the influence of Heredity.

Out of the records of 205 cases, which I have read in the preparation of this study, I find that no less than 110 are to be found in the family groups.

This fact that practically one half of the cases give evidence of the influence of Heredity at once suggests the possibility that if family histories in this disease were more carefully inquired into ~~that~~ more such cases would come to light. The chief points which emerge from an analysis of these family cases are the following.--

1. The number of individual members of families mentioned in these records is 207, and of these

110, or just over 50 per cent., are sufferers from the oedema, which is indisputable evidence of the potency of ancestral influences at work.

2. The study of the statistics of these cases brings into extraordinary clearness the shockingly bad prognosis in regard to life that is the lot of a member of a family in which Angioneurotic Oedema is prevalent. Out of 110 cases, no less than 30, or 27.2 per cent. have come to a fatal termination with symptoms of suddenly developed Asphyxia, resulting in the majority of the cases there can be but little doubt from Oedema of the Glottis.

3. The existence of the peculiarly high-strung nervous temperament is commonly noted in this family group as in solitary cases; yet in these families there is almost a complete absence of any gross functional or organic disturbance of the Nervous System.

4. There is no indication of any definite descent of the morbid condition in the male or female line, exclusively.

5. The disease, as a rule shows itself in early childhood, or at any rate before puberty in one or other of its manifestations. It thus affords a contrast to the solitary cases where the average age is 21.

6. It may safely be asserted that in these family cases, gastro-intestinal symptoms, often of an extremely painful and distressing character, are quite

as frequent manifestation of the disease as the oedema itself. It should also be noted here that the gastro-intestinal disturbance may for long precede, or may come later in life than the oedema. The proportion of solitary cases in which digestive troubles are noted is I find about one -third.

7. It would seem that in a number of these cases there is a tendancy for the disease to manifest itself at an earlier period of life in the succeeding generations.

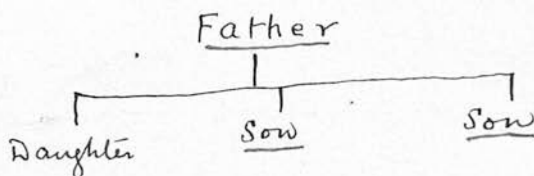
8. In regard to sex, the proportion affected shows 67 males as compared with 39 females, and of the fatal cases there are 18 males and 8 females.

In the genealogical tables I have underlined the affected cases with red ink, and the fatal cases are indicated by a cross in red ink following the name.

Observation of Valentin.

(Berlin klin. Wochensch.,1885, Bd. X., p.151.)

The first two cases of Dinkelacker concerned a watchmaker and his son. The younger son, not then born, is now (1885) four years old and has similar symptoms of periodic Angioneurotic Oedema. Valentin watched the cases for a fortnight, and saw several out-breaks. The elder brother had had his attacks since he was a few weeks old. The other member of the family, a daughter, escaped.



OBservation of Strübing.

(Zeitsch. fur klin. Medizin., 1885, Bd., IX., p. 381.)

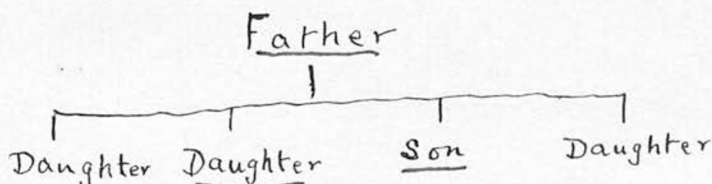
Case. 1. A High School teacher, aged 70, had at the age of 25 for the first time, after a chill, pain in swallowing. In from one to two hours he became very bad, was hoarse and had difficulty in breathing. In another half hour he was much easier and was quite well the next morning. Then the upper lip used to be swollen in the mornings, and then the lower one and the eyelids. The swellings would take several hours to reach their height, and in three days he would be well again. When the swelling appeared in the skin of the neck he was troubled with difficulty in swallowing and with breathlessness. After having freedom from pharyngeal and laryngeal difficulty for some years, he had a severe attack in September, 1883 during which he was seen by Strübing. There was great inspiratory dyspnoea which had reached its height in about fifteen minutes. The symptoms of stenosis were very marked.

Scarification of the Glottis was out of the question owing to his great physical distress. A few minutes later the symptoms of stenosis had passed away, and in six hours from the beginning of the attack there was no trace of oedema of the Glottis to be seen. Then came on oedema of the face, lips, eye-lids, and of the Penis and Scrotum, lasting about four days.

From the age of 26, he had had attacks of vomiting every four to six weeks. It was usually preceded for a few hours by gradually increasing pain, and he would then as a rule vomit for four or five hours. Sometimes the attack would last for twenty-four hours, and he would vomit as many as 20-30 times or more. He would feel heavy and stupid during an attack, but as a rule he would be almost quite well the next day.

Case. 2. Son of the above. A healthy lad of 16. Similar attacks of oedema mostly occurring on the extremities, as the reult of slight knocks, or such injury, starting, say, in the hand and wandering up the forearm to the elbow, taking a few hours to reach height, and lasting one to two days. Since three years old he has also had similar attacks of vomiting to those of his father.

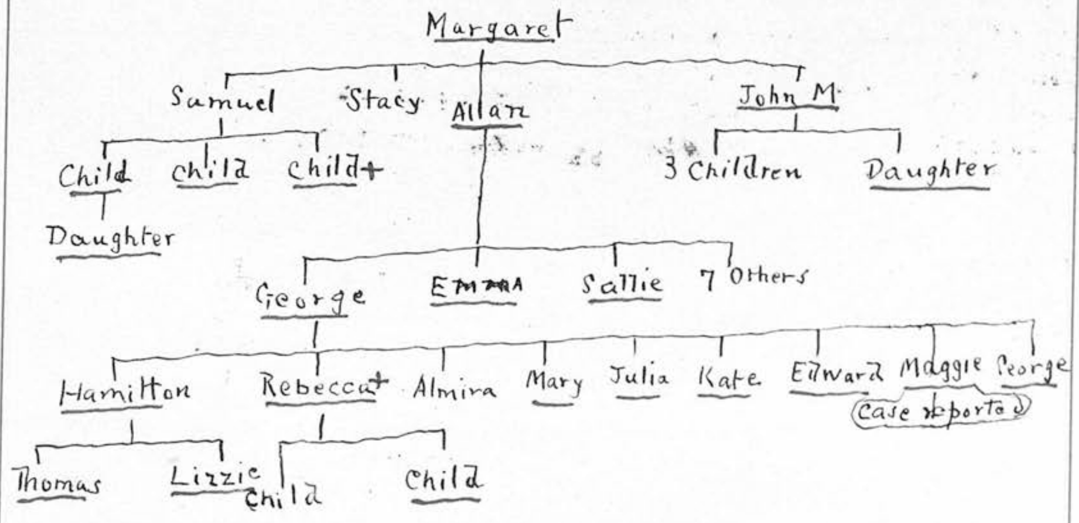
Case. 3. Sister of the preceding case. Since age of 22 at intervals of about a fortnight had had also similar attacks of vomiting, and in later years has had several attacks of oedema of the eye-lids.



Observation of Osler
(American Journal of Med. Science,
1888, Vol., 95.,p. 362.)

A married woman, aged 24, (referred to as Maggie in the genealogical table) had had frequent attacks of oedema mostly affecting the lips, which have at times been so swollen that she could not open them herself and milk to feed her had to be poured in from above while the lips were held apart. She has required to have her ring filed off to prevent gangrene of the finger during an attack of oedema. The swelling comes on very rapidly, and lasts from one to four days. There is not much itching but a feeling of tension and stiffness. There is no pitting when the oedema is fully out, but there is a slight sign of it when the swelling is subsiding. When the attacks are bad, they are accompanied with colic, nausea, vomiting, and hehdache; but no fever. Rarely two weeks pass without an attack. She does not think that food has anything to do with bringing them on.

From the grandfather of this patient, a man of 92 years of age, Professor Osler obtained the remarkable history of this affection being present in no less than 22 members of his family throughout five generations. Her grandfather thought that the trouble had begun with his mother, who was born in 1762 and died in 1834. She had attacks of oedema in her hands, feet, face, and neck from an early age. Once she nearly died from an attack of shortness of breath. She also had the attacks of colic at the same time as the oedema.



Observation of Fritz.

(Buffalo Med. and Surg. Journal,

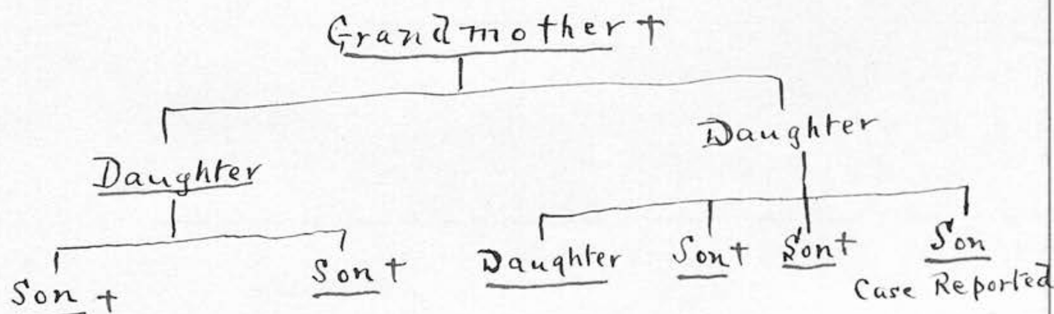
1893-94. Ref. Ouvray's "Oedemes

Familiaux" These de Paris,

1905-06, p., 43.)

A man,,aged, 33, fell and bruised right temple. Soon after ~~Soon after~~ the left eye-lid began to swell and the eye became completely closed. From there the oedema spread to the cheeks, lips, and neck, and when he was brought to the hospital there were signs of cyanosisand dyspnoea, almost complete aphonia, and free mucous expectoration. The uvula, the left tonsil and the left part of the Glottis were oedematous. During the night oedema appeared in the right side of the face. The following day it went from the face, and appeared in the right foot and ankle. His lungs and heart were normal. The urine was free from albumen or sugar. THE general health was otherwise thoroughly good. Since the age of four he has been subject to oedematous outbreaks following blows or knocks, and the parts mostly affected are the extremities or the eye-lids. Drinking on an empty stomach will often induce an attack.

His grandmother died of Oedema of the Glottis, which has also been the cause of death to two of his brothers and to two of his cousins.

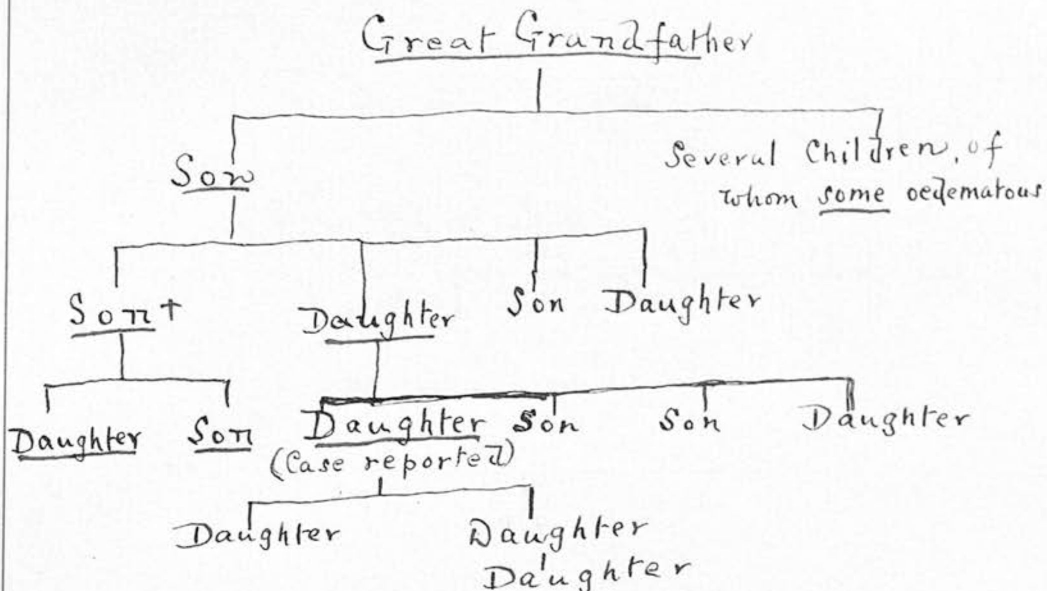


Observation of Varian.

(Medical News,--American--1896, Vol.,69, p. 239.)

A married woman, aged 44, relates that when she was still a child, her mother noticed periodical attacks of blanching of the skin, and vomiting. The patient could not remember a time when she did not suffer from recurring attacks of oedema, following gastralgia and vomiting. The attacks begin with a general feeling of malaise and pain, and soon some part of the body, usually the hands, face, feet, arms, shoulders, chest, will become very oedematous. Often simultaneously with the oedema will occur purple rings upon chest, neck, arm, and hypogastric region. They mostly occur, however, just after the oedema has subsided. Mental emotion, especially anger, is capable of precipitating an attack. From twenty-four hours to two days, after the swelling begins, she is taken with a severe pain, usually in the region of the stomach, but sometimes of the bowels. She describes the pain as being severe, often terrible, and prostrating. It is followed by nausea, vomiting, and often severe retching. After freely vomiting, the oedema and pain disappear, an attack in the morning often failing to incapacitate her for her work in the afternoon. Her attacks occur about every fortnight since her child-bearing period, but previous to that every week for some weeks, then skipping several weeks. Nine weeks is the longest spell that she has ever known. The oedema sometimes occurs without any vomiting or pain. The attacks are always more severe when occurring at a menstrual period, and they were always worse during her times of gravidity, and the menopause has not affected their frequency in any way.

Her mother had similar attacks, but not so severe from childhood, An uncle, on her mother's side, who was also afflicted died at age of 42 from Oedema of the Glottis. Its presence in other members of the family appears in the adjoining table.



Observation of Schlessinger.

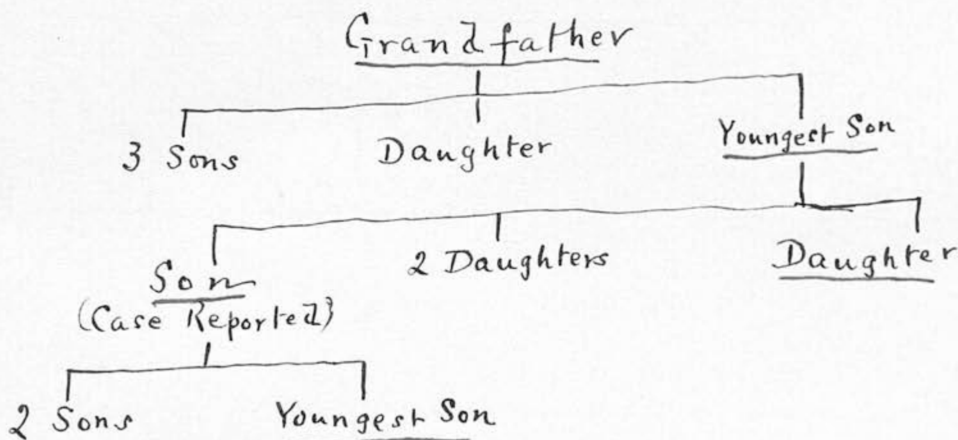
(Wiener klin. Wochensch. 1898, Vol. XI.

p. 334-338.)

Martin J. had had attacks of Acute Oedema since age of 7, he at time of observation being 44. He was by occupation a merchant. Since 22, the attacks have increased in frequency, at first every six months, but later, every ten or eleven days. A feeling of mental depression or excitement often precedes an attack, and there is often a premonitory exanthematous appearance in the shape of a red ring or branched figure, which comes on some part of the body, but which is rarely wide-spread. This peculiar eruption disappears after six to eight hours, and is succeeded by a swelling, which developes in a few seconds, as a rule, in the limbs of the right side and in the Scrotum and Penis. In the first attack, the Scrotum sank like a stone, and attained the size of a child's head in a few seconds. He has a feeling of tension but no pain, and the skin, though at times slightly red, is mostly pale. At the same time he has a feeling of pain in the stomach, which is tender to pressure, and also vomiting. These feelings last for three days. Food has no effect in inducing an attack. Beyond a slight Mitral Insufficiency, his general health was sound. There was nothing abnormal in his urine.

The grandfather, on his father's side, suffer-

ed from the same sort of attacks from the age of 20 years to the time of his death, over 80. The father of the patient enjoys thoroughly good health, except for the oedema, which also began at the age of twenty. He also has the aame prodromal eruption and cerebral excitement or depression. A younger sister of patient suffers in much the same way, and his youngest son, at 16, is giving some signs of the prodromal eruption, but so far has not had any oedema.



Observation of Mendel.

(Berlin klin. Wochensch., 1902?

No. 48, p. 1126).

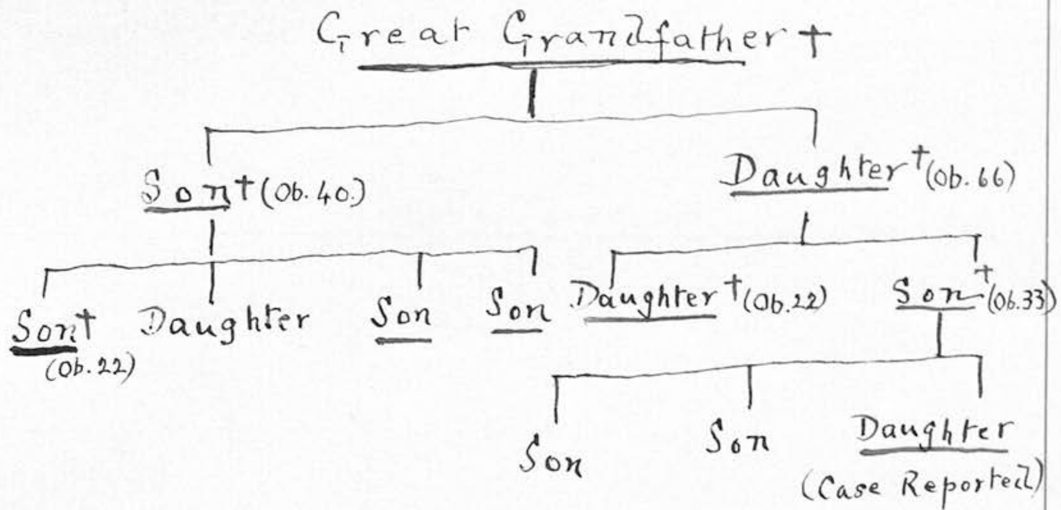
A. H., a girl of 18, was brought to him with a large swelling of the left arm, extending from the finger tips to the elbow. Her mother reported that the girl had suffered from her earliest years from large swellings in different parts of the body, at irregular intervals, in arm, leg, neck, half or whole of face, private parts, and in mucous membrane of the mouth, and in the eyes. They would come within some hours and disappear as quickly, without leaving any trace. AT times, though very rarely, they may last for 5 to 8 days. They mostly come without any known cause though they may come, but not invariably, after, a fall blow, knock, or other slight injury. Her general con-

dition was good. No anaemia, or Hysteria, or other nervous disorder. Internal organs sound, and urine normal. No Dermatographia, or trace of Urticaria, or any other skin eruption. The arm was swollen (as is well shown in the photograph which is published with the paper), yellowish white in appearance, feeling cooler than the neighbouring skin; no sign of inflammation. There was, if any, but the most trifling sign of pitting on pressure. The parts were not painful to pressure. The patient complained only of a feeling of tension and weight. No sensory disturbance. Patient cannot extend the fingers owing to the swelling,- and cannot lift the forearm without help of the other hand, owing to the weight. The swelling began as a small hard lump at the elbow, and within twenty-four hours had spread all over the forearm. The general health seemed to be in no way affected. The patient returned two days later, and arm was then quite normal. Her body weight, under exactly the same conditions had decreased from 118 lbs. to 115½ so that the oedematous fluid must be reckoned at more than a litre.

The great grandfather of the patient died suddenly of suffocation. His son and daughter both had the oedema, and they both also died of suffocation. A daughter of this woman died in a similar way at 22, and the patient's father at the age of 33 years, one morning complained of pain in the chest and shortness of breath and of cough. The doctor supposed he had inflammation of the lungs, although there was no fever; but, in the evening, he became hoarse, the dyspnoea increased, and he was dead in a few minutes

The brother of the grandmother died at 40, from suffocation after the extraction of a tooth. HE left four children, among them three sons, one of whom succumbed to the disease at 22, whilst the two others are alive at the ages of 51 and 48, and both suffer from the malady almost every week, and are in constant dread of death from suffocation whenever the oedema attacks their throat or face

OF 12 persons, in four generations, 9 have been attacked, and of this number 6 have succumbed to it.



Observation of Griffith.
(British Med. Journal, 1902, June, 14,
p. 1470.)

The patient was first seen when she was 18 years old, in 1886. She was then suffering from Dysphagia, Dyspnoea, hoarseness, and oedema of hand and arm. The oedema involved the Epiglottis, the Ary-epiglottidean Folds, obscuring the view of the Vocal Cords. She had had these transitory oedemas in all parts of her body since she was a child. Her general health had otherwise been good. She was under the observer's professional oversight from 1886-1902. The tongue and the mucous membrane of the mouth were sometimes the seat of the oedema. She had an alarming attack of Dyspnoea in 1890, and again in 1891, on which occasion, accompanying a toothache, was a swelling on the same side of the face. The swelling increased and when he saw her at 11 p.m., her face was swollen out of recognition, her voice was hoarse, and the Dyspnoea was very great. The Larynx was readily examined, but all that could be seen were three rounded lumps, pale, tense, and jelly-like, which represented the mucous membrane over the Epiglottis, and the two Arytenoids, while the False and the True Cords were completely concealed. The next day she was much better, the voice clear, and the swelling on the face manifestly subsiding; and by

the following morning, the swelling was nearly all away and the Larynx was normal. There was scarcely a sign of any general disturbance throughout.

On February, 20th., 1902, at 10.30 in the morning she told her mother that she had some swelling in her throat; but she thought that it would soon be better. At noon, her husband found her sitting on the floor in the act of preparing to spin a humming top for her child, and to all appearance she was not suffering from Dyspnoea. Suddenly she dropped the top, tried to speak, but could not, clutched her husband's throat as if to indicate the seat of her trouble, got blue in the face, and died almost at once.

The autopsy showed the Larynx to be very oedematous, tense and pale, its sides being in contact. Transverse sections showed that not only was the mucous membrane affected; but also the underlying connective tissue and the muscles. The oedematous fluid was serous, untinged with the colouring matter of the blood, and the tissues covering the two cords were decidedly affected.

The father of the patient had had the same attacks of oedema from infancy. At 20, he had an attack in his throat, another one a few years later, and in the third attack, at 29, he died from Asphyxia. The mother, who entered the room just as her daughter was dying, said that it was in exactly the same way that the father had passed away.

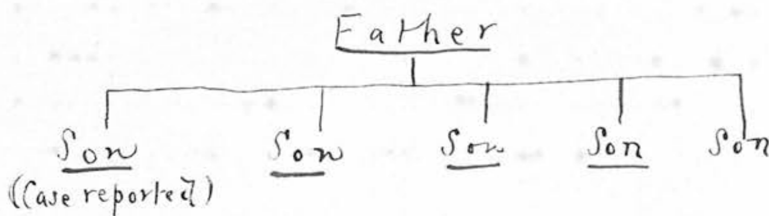
Father † (Ob. 29.)
|
Daughter † (Ob.34.)

Observation of Courtade.
(Archives internationales de Laryngologie,
Nov.-Dec. 1903. Ref. in Ouvray's
These de Paris, 1905, p. 32).

Patient, when seen in 1900, was 55 years of age. He had to undergo Tracheotomy in 1898 for oedema of the Larynx, following on the bite of a mosquito under the left eye causing oedema of the face and neck. The operation had to be repeated in 1900 on account of threatened Asphyxia from some cause unknown.

At 12 years of age he had an attack of convulsions, and at 15, an attack of acute Articular Rheumatism, which lasted about two weeks. Since then he has been subject to these sudden attacks of oedema, which reach their maximum in 24 hours, and quickly disappear. If he walks much his feet swell, and if long seated, the buttocks have the impression of the seat on which he has been resting. One day, in passing a bicycle in a difficult bit of road he had to use more than usual force to grip the handle-bar of his own machine, and next day the two hands were swollen. He would get oedema of the face, if he rested his head upon the table to sleep, and the least knock on the face would bring it on in this part of the body. These attacks occur about a dozen times a year. He has digestive troubles, characterised by abdominal pains, without Diarrhoea, and followed by the vomiting of blood. There does not appear to be any connection between the digestive attacks and the oedema.

His father had for the first time at 57 oedema of the Scrotum. Of four brothers, three, at ages of 30, 32, and 33, at time of record, have had attacks of sudden oedema in limbs and other parts of the body after exhausting effort or the result of slight knocks.



Observation by Ensor.
(Guy's Hospital Reports, 1904, p. 111).

Case 1. Ezekiel L., aged 66, was liable to sudden swellings in the throat and about the body. On October, 16th., 1895, he was returning home from his work, and was seen by a shepherd at 3.50. THE shepherd spoke to him and he seemed to be in his usual health. At 4.45 p.m., he was found dead on the road-side, a little further on the road from where he had met the shepherd. When Ensor saw the body, half an hour later, it was lying prone, the hands were clenched, and the face and the visible mucous membranes were of a purplish colour. The tongue was not swollen. He could not secure a post mortem examination.

Case 2. Henry D., aged 24, nephew to Ezekiel L., had suffered from several attacks of oedema. On October, 16th., 1895, he was sitting at supper, when he heard of his Uncle's death. When told the cause he was much agitated, and expressed the belief that he himself would die in the same way. Early on October, 18th, 1895, two days later, Ensor was sent for, and on arriving found him dead. He had been suddenly attacked with Dyspnoea, and was dead in a few minutes. His mother said that several times during his life he had been threatened with suffocation. He would never go to sleep if his face was oedematous, for fear it might spread to his throat.

Case 3. Sarah L., aged 41, a niece of Ezekiel L., had since her childhood been liable to attacks of localised oedema. On June, 29th., 1891, while occupied with her household duties, her face became swollen. As, however, this had happened before without other alarming symptoms, she did not think much of it. As the oedema increased, she went to her sister's house, where she had some tea. She then went up stairs, and a few minutes later she called out that "it was going

to her throat, and she was sure it would choke her". Her face was then more swollen, and her eyes were closed with the swelling. Her breath became more laboured, and she died of suffocation a few minutes afterwards.

Case 4. Emily L., aged 13, daughter of Henry L., died cyanosed after 12 hours from the onset of acute lung symptoms. Ensor was called in to see her on October, 10th., 1895, a little while before she complained of shortness of breath and became rapidly worse. The physical signs were those of acute Bronchitis, and there was moderate Pyrexia. He could not determine if any portion of the lung was solid. She died that evening. The child had been subject to attacks of oedema.

Case I. a. Mother of Case 2., he attended for a severe attack of oedema of the tongue, which caused embarrassment of the breathing.

Case. 2. b. he attended in a severe attack of abdominal colic, to which he had always been liable, as well as to oedema. He had been thrice threatened with suffocation. He was the father of case 4.

Luke L., was the first member of the family to be affected, as far as is known. He was found lying dead on the floor of his house, when at the age of 70.

Besides the fatal cases already mentioned in this remarkable family history the following are deserving of note.

Annie L., aged 16, In early evening one of her hands became swollen. She woke in the early morning with a feeling that she was choking, and she died of suffocation an hour and a half later.

William L., 66, had an attack of oedema in his hands in the early morning, but he went to his work as usual. He returned home at mid-day as his throat was becoming affected, and he died of suffocation at 1.45 before medical aid could reach him. He had often suffered from oedema and colic, and his daughter said she had frequently seen his face so swollen that he could not see.

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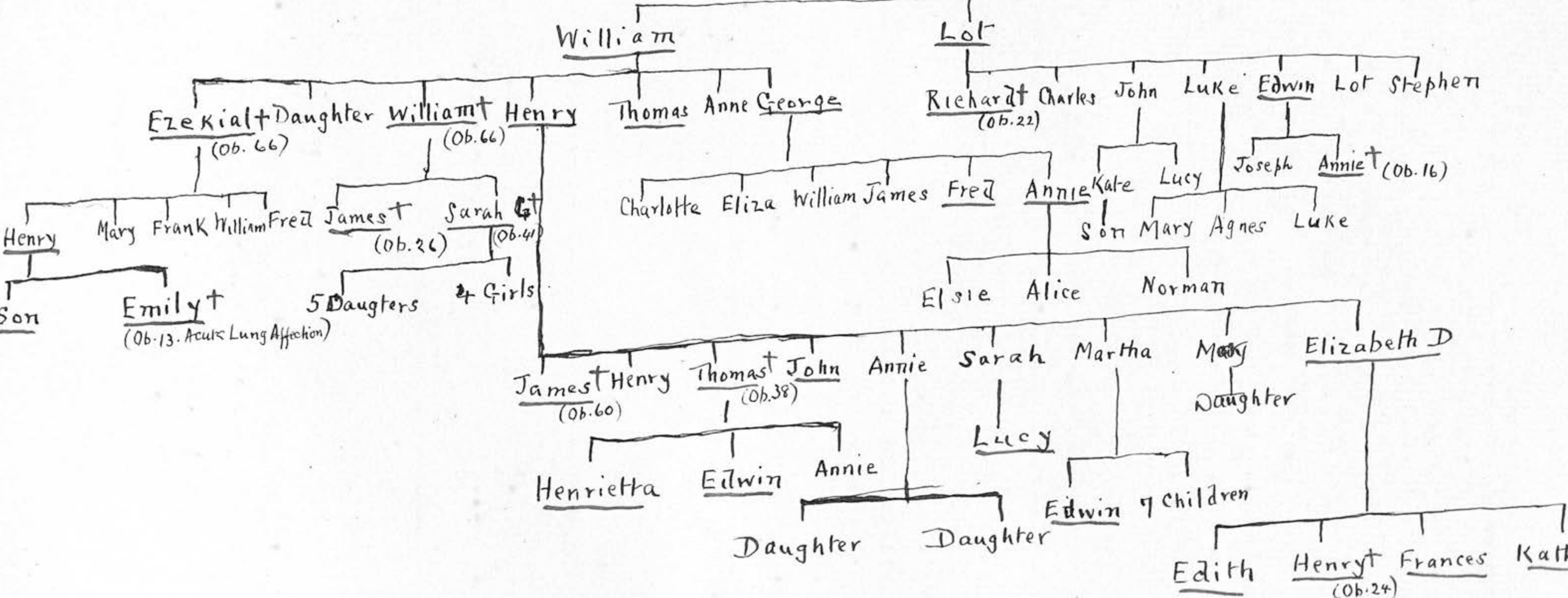
Thomas L., aged 38, who suffered from oedema, was found sitting on the side of the road, gasping for breath, as he was returning home from work. He was just able to say that he had the swelling in the throat and was dead in a few minutes.

Four other cases, which have ended fatally with like symptoms of suffocation, making the large propor- of 12 out of 33 individuals, who have suffered from Angioneurotic Oedema, in a family group which comprises 80 members.

Genealogical Tree of Ensor's Series



Observation of d'Apert and Delille.
(Soc. Medicales des Hopitaux. Ref. Ouvray,
Oedemes Familiaux, These de Paris, 1905-6).

Case 1. Boy, aged 9, was brought to the Hospital, Bretonneau, when Ouvray was in the service of the out-patient department, with symptoms of marked Dyspnoea. The Uvula and Glottis were very oedematous and there was swelling under the chin, and over the back of the right foot. These swellings were hard to pit on pressure. His heart and kidneys were quite sound. A feature of interest about this case was the fact that he was brought by an uncle, who had been subjected to Tracheotomy for a similar trouble, and he recognised the possibility that the child was a victim to the same trouble. Since age of 4, the boy had had oedema of the arms cheeks and forehead, and more rarely of the lower limbs. Four months ago, he had oedema of the face succeeded by swelling of the tongue and palate, and inspiratory Dyspnoea, indicating Oedema of the Glottis. Since then a succession of these attacks about every fortnight, together with pains in the stomach and nausea.

Case 2. Uncle of patient, 40 years old. Since 10 years old, every 8-10 days, oedema of limbs, face, genital organs, pharynx and larynx has made its appearance, lasting about a day. A slight blow will often s start the oedema, but not invariably. Three years ago, he was tracheotomised, during an attack in the Larynx, and the wound was re-opened during another attack. Since then he has worn a tube constantly.

Case 3. Elder brother of previous patient and father of the first, aged 38, a wood turner, had good health up to 28. Since then every two months, one month, or fortnight; he has had oedema of the backs of the hands, one or both, which last one to two days, or may be three. Towards the end of an attack, a state of general malaise, and nausea, followed by bil-

ious vomiting. By his first wife, who was nervous, and delicate, he had the two children mentioned as cases 1 and 5, and by his second wife, who was in good health, two daughters, 2½ years and seven months, who are so far healthy.

Case 4. Younger brother of the previous patient, 30 years old, who, since age of 10, every two or three months, has had oedema of feet and hands, lasting for a day.

Case 5. Son of Case 3, aged 11 years has since age of 7 had every three to four months oedema of arm, lasting some hours. It is sometimes accompanied by pain in the stomach and nausea.

From the above qoted work of Ouvray, I take the following references to cases, which I have not been able to consult in their original sources.

1. Observation of Falcone. (Gaz. de gli Osped., 1886). Child of 7, and grandfather had Angioneurotic Oedema, father was free.

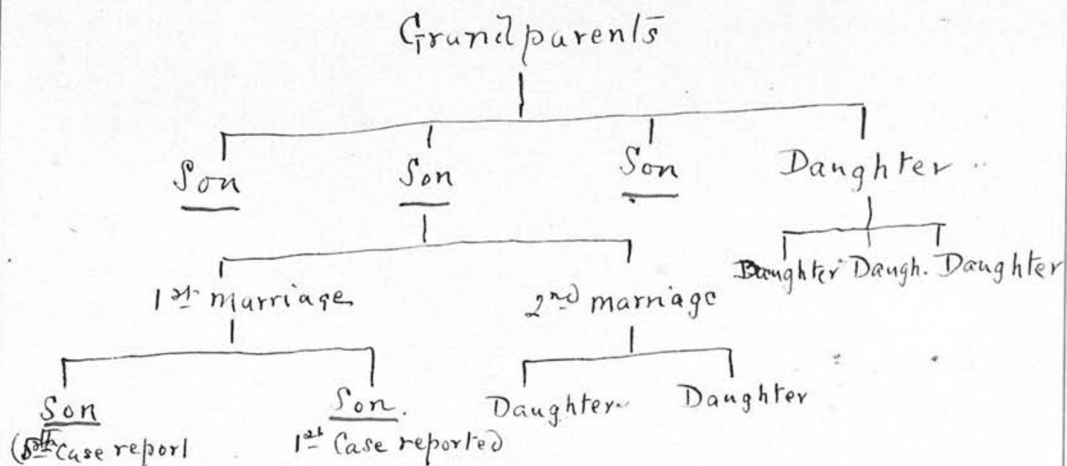
* 2. Observation of Krieger.† (Med. Oboz., 1889). Man, aged 25, and mother both affected.

3. Observation of Smith, (Med. News, 1889). Case of a young woman and her mother.

4. Observation of Roy. (Med. Record, 1894). Case of mother and daughter.

*. I find reference by Mettler to fact that this patient was found dead in bed and post mortem exam^n showed Oedema of Glottis.

Series of d'Apert + Delille



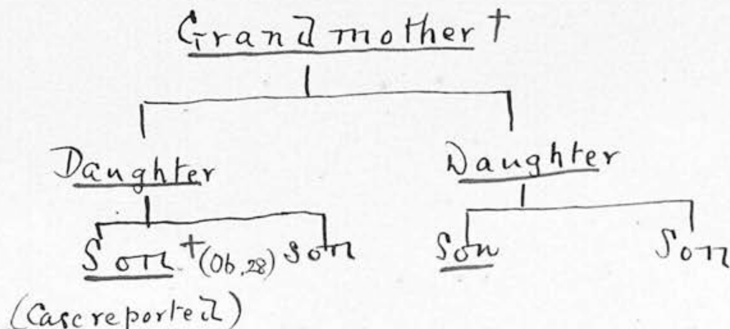
Observation of Prior.

(Australasian Med. Gazette, 1905, p. 117).

Patient, aged 28, was admitted to hospital as an imbecile. He had constant tremors of both hands, otherwise normal condition of health. He suffered from recurrent attacks of oedema of body, lip, hand, arm, or penis. No periodicity noted. The presence of the oedema did not appear to affect his mental condition. They swellings would remain from 24-48 hours. While in hospital, at 3 a.m., one morning, his lower lip was noticed to be swollen. At 7.30, there was extensive swelling of both lips, the face,,and neck. He was then breathing without difficulty, and his voice was quite natural. At 10 a.m., he had a sudden attack of Dyspnoea, and was dead in a few minutes.

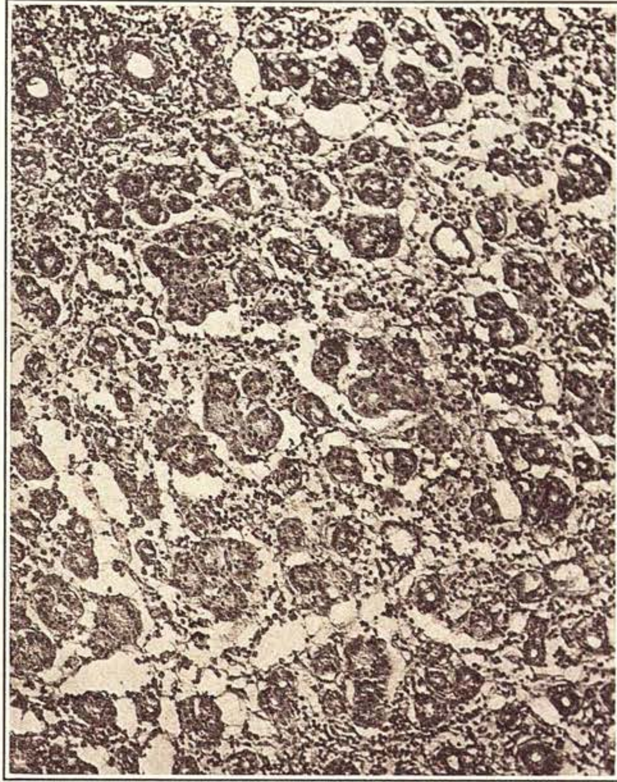
A partial post mortem examination was made within 24 hours. Besides the face, the Epiglottis was swollen and pale, being about three times the normal s size. The mucous membranes, covering the Thyroid cartilages, were pale and swollen so much that they nearly touched each other. The Trachea was congested.

The patient's mother said that his maternal grandmother was always subject to large white swellings, which came on with very slight causes, and she died suddenly from "swelling of the throat." The mother of the patient has had her tongue greatly swollen. A maternal aunt, and one of her sons suffers from the same sort of swellings as the grandmother. His youngest broG suffers from Epilepsy, but no other neurotic tendancy could be found in the patient's family.



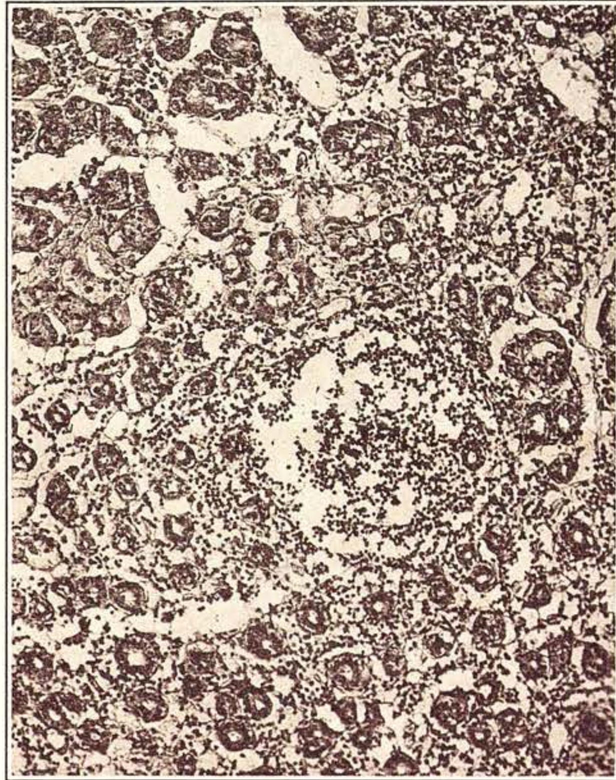
Although without permission to publish, I have taken the liberty of appending to this account the microphotographs, accompanying the paper of Morris, as they contribute greatly to the explanation of this important observation.

Fig. 2.



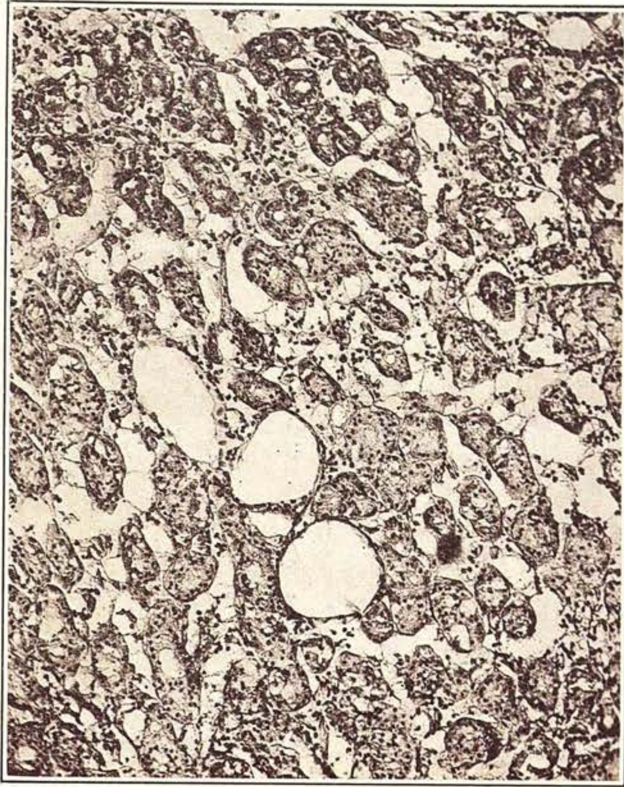
Portion of gastric mucosa removed by stomach-tube from Case II. of angioneurotic œdema. Extreme œdema of stroma.

Fig. 4.



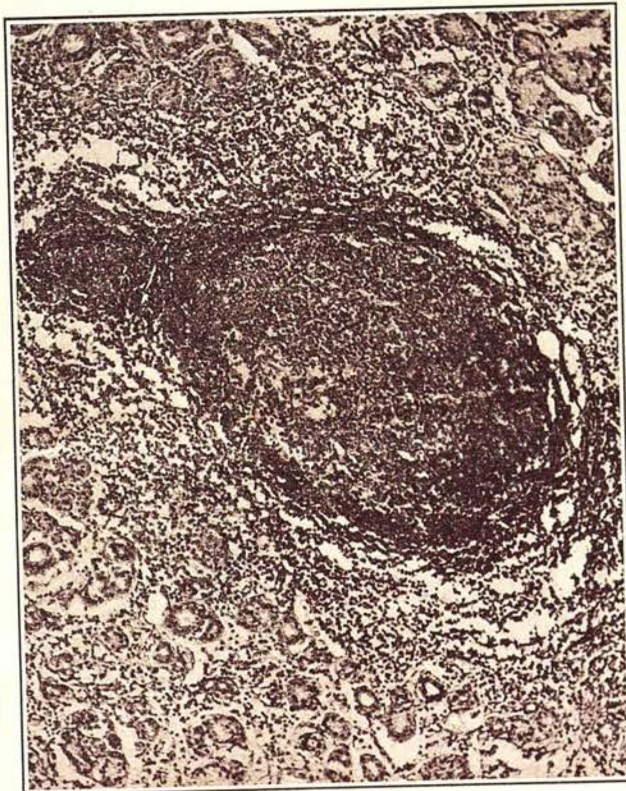
Portion of gastric mucosa removed by stomach-tube from Case II. of angioneurotic œdema. Small lymph follicle, showing marked œdema.

Fig. 3.



Portion of gastric mucosa removed by stomach-tube from Case II. of angioneurotic œdema. Extreme œdema. Great dilatation of lymph spaces and vessels.

Fig. 5.



Portion of gastric mucosa removed by stomach-tube from Case II. of angioneurotic œdema. Large lymph node, showing œdema of the peripheral and central portions.

Observation of Morris.
(American Journal of Medical Sciences, 1905,
Vol. 130, p., 382-386).

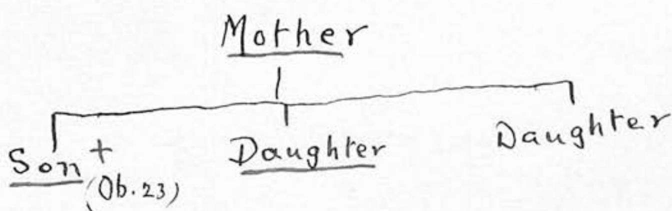
The patient a man, aged, 21, a shorthand writer, was admitted to the Michigan University Hospital, in 1903. He was complaining of swellings in hands, legs, larynx, and troublesome pains in his stomach. He first noticed the swellings in his hands at the age of 12. At 17, he had "Scarlet Fever" with Nephritis" and had at the same time an attack of Oedema of the Glottis; for which tracheotomy was performed. He then had good health until July, 1903, when tracheotomy was done a second time. He had awakened in the morning with a swelling under the shoulder blade, at 4 p.m. his throat was affected, and at midnight tracheotomy had to be again resorted to to relieve him. On admission to the hospital he showed signs of oedema of the larynx; but his chief complaint was of the pain, nausea, and vomiting, from which attacks he was accustomed to suffer atintervals of three or four weeks. While he was receiving lavage for this condition, a piece of the Mucosa of the stomach became detached and it was brought up with the tube, and its microscopical examination, referred to in the Chapter on Symptomology, demonstrates the oedematous origin of the gastric troubles in these cases.

After leaving the Hospital, he had many attacks of oedema, especially after slight knocks, and once or twice he had signs of laryngeal obstruction. When the patient retired to rest on Jan., 3rd, 1905, he was apparently in good health. His parents, however, were aroused by hearing a noise, and on entering his room, they found him ~~dead~~, propped up in bed, with the front of his night shirt covered with blood. He died before

the doctor arrived. The autopsy showed an extreme grade of oedema of the larynx, involving the epiglottis, the aryteno-epiglottidean folds, and the true and false vocal cords, the ventricle of the larynx being obliterated. There was also intense oedema of all the loose laryngeal tissue above the true cords, but below the latter, there was no evidence of oedema. The tissue at the sides of the aryteno-epiglottidean folds was also markedly oedematous.

Photographs of the oedematous parts, attached to the original paper show in a very clear manner the deep-seated invasion of the oedema, and showt too that the muscular movement of the parts may be interfered with, as well as the blocking of the passage by the swollen mucous membrane.

The mother of the patient has since childhood suffered from attacks of oedema in the hands, and the signs of the malady have been much more pronounced since the death of her son. and a sister of the patient is liable to attacks of oedema of the face after slight blows.



S Y M P T O M A T O L O G Y.

With special reference to the cause of the Gastro-intestinal Symptoms.

The cardinal features of the oedema as it shows itself in the skin have been fully illustrated in the cases presented, and may be summarised as.--

Acute development, in a few hours; transient existence, measured at the most by several days. More or less localised from the surrounding parts. Often multiple in number. The colour of the skin unaltered, or if slightly red, not accompanied with itching. No sign of pitting on pressure. Usually free from pain on pressure, and no subjective sensations except a feeling of discomfort through tension of the parts. No perceptible effect left on the tissues after it has passed away. It is rarely symmetrical in its distribution. It appears on all parts of the body, with perhaps the exception of the hairy scalp, selecting mostly the parts not covered by clothing.

The symptoms as they manifest themselves in the mucous membranes, visible to inspection, as in the lips, tongue, pharynx, buccal cavity, and the larynx have all been referred to in connection with the cases quoted. In regard to mucous membranes, not open to direct inspection, it has been from the first suspected that they were due to an oedematous out-break anal-

agous to that of the skin and the other mucous membranes. It has remained, however for the investigations of the last few years to place this fact beyond a doubt, and to establish the certainty that the symptoms of colic, nausea, vomiting, and the lesser digestive troubles are inseparably linked to the oedematous basis of this malady. No historical survey of Angioneurotic Oedema would be complete without a somewhat detailed reference to the facts on this point from the valuable paper of Morris. The details, regarding the patient's general symptoms, and the singular way in which a piece of the mucous membrane was detached during an acute attack and brought up by the stomach tube, are given on p. 57 of this Thesis. I shall now quote in an abridged form the report of the pathologist upon the specimen.--

"The piece of tissue was put in strong alcohol at once when it came from the stomach. IT measured 13 mm. by 7 mm. and was 4 mm. in thickness. It was then stained, and examined microscopically. It was prrbably from the pyloric end, as a few parietal cells were found in the glands and as numerous lymph nodes were present, the character of the sections correspond-in general to that of glands from that end of the stomach. The entire tissue presented the picture of an extreme oedema of the interstitial tissue, the lymph spaces and vessels being enormously dilated, the cells of the stroma being separated by wide spaces or vacuoles and the supporting fibres in many places separated into their ultimate fibrils. The glands as a rule were somewhat or contracted from their basement membranes and vacuoles were found in some of the epithelial cells. No excess of mucous formation. The oedema was chiefly confined to the interstitial tissue, hence the suspicion of the tissue having been water-soaked, which was entertained at first sight, was not supported. The appearance of the vacuoles in the stroma and

the dilatation of the lymphatics gave, moreover the impression of a fluid confined under pressure. A very finely granular precipitate staining red with eosin in the lymphatics and about the edges of the vacuoles was taken as evidence of the slight albumin content of the fluid. Numerous small round cells were present in many areas, to a greater extent than is usually found in normal gastric mucosa. Many of the stroma cells contained vacuoles and were swollen and spherical. T The smaller lymph nodes showed likewise an extreme oedema, the cells being widely separated. In the larger lymph follicles the oedema was most marked about the periphery of the node and in the central portion, the cells in these places being widely separated. From all the appearances a diagnosis of extreme oedema of gastric mucosa, non-inflammatory in origin."

In regard to the possibility of the tissue having been incarcerated in the stomach tube, Morris says "It can be dismissed as the removal of the test meal with the subsequent lavage was performed by a most experienced operator. As the piece of tissue was undoubtedly obtained from a wound inflicted by the end of the tube at the time when the stomach was being washed, the conclusion is forced upon one that there was an acute, non-inflammatory oedema of the gastric mucosa.

Another most important case bearing upon the same question is the following.--

Observation of Harrington.

(Boston Medical and Surgical Journal, 1905,
Vol. 152, No 13, p. 363.)

Girl, aged 26, a factory hand, had the fist attack 15 years before. The swelling came on hands and feet at intervals of not less than three months, and for the last few years not more than two weeksś intervalval. Now and then the face and as far down as the clavicles is swollen. The lips are large and eating in attended with great difficulty, and swallowing of liqthen causes nausea. The lips usually swell suddenly and remain swollen for several days. There is a lia-

bility to periodic attacks of abdominal pain, often in the region of the gall bladder. Sometimes the pain extends into the lower half of the abdomen without radiating into the back or the shoulder. The attack usually lasts 24 hours, and is always marked by nausea, vomiting and headache. The vomit is liquid, green, never blood-stained and amounts to one or two quarts at a time. She has never had jaundice. As from the localisation of the pain there was the possibility of the existence of biliary colic her consent was obtained and an operation was performed during an attack.

There was a good amount of clear, free fluid among the intestines filling the Pelvis. The intestines themselves were engorged with blood, and so red that a mild Peritonitis was at first supposed. There were no haemorrhagic areas in the intestinal walls; but at a point a short distance from the Ileo-caecal Valve a cylindrical enlargement of the Ileum, 2½ inches long, was brought to light. It entirely surrounded the gut, increasing the bowel circumference to twice its ordinary size. The swelling was apparently in the bowel wall, elastic to touch and did not pit on pressure. It could be readily understood how such an infiltration could derange peristalsis action of the intestine The Appendix was removed and was normal. The lower border of the stomach was half an inch below the Umbilicus. The Pylorus admitted the tip of the index finger. The engorgement of the intestines and the free fluid were undoubtedly explained by the effort of the Peristalsis brought on by the effort to force down the lesion which was actually in the intestinal wall.

That portions of the respiratory tract beyond the larynx may give rise to symptoms owing to localis- oedematous effusions was long ago suggested by Jamieson,[35] and later by Schlessinger[68] and its probability is confirmed by a case of Ensor's[23] and also of Diller,[16] and more especially by a very convincing one reported by Quincke and Gross (Deutsche med. Wochensch. Bd. 30, 1904, p. 12.)

Analogy would suggest, too, that certain Asthmatic symptoms may be developed upon the same base. THE hypothesis of Sir Andrew Clark that Asthma is caused by tumefactions of the mucous membrane of bronchial tubes has much to be said in its favour. Goodhart[29] while inclining to the hypothesis of spasm of the muscles says that the other one is about equally as g good. Packard[60] has collected some 37 cases of Asthma in close association with Urticaria , which is, of all diseases, the one in closest alliance with Angioneurotic Oedema.

THAT symptoms may also arise from similar effusions in the brain is contended for by Osler,[56] Ullmann[78] and others.

Intermittent Effusions into the Joints have also, with sound reasoning, been claimed eligible for inclusion among the symptoms of this malady by Schlesinger[68] and Mendel.[88]

COMPLICATION WITH OTHER DISEASES.

Quincke,(62) from the first made it perfectly clear that a very intimate alliance existed between this disease and Urticaria. Both are acknowledged generally to be vaso-motor Neuroses, and the elements of the skin they involve are practically the same; although if Unna's(76) contention is correct Urticaria concerns chiefly the true skin, while Angioneurotic Oedema makes its influence primarily felt in the subcutaneous layer, and only by secondary extension involves the skin. Still, in any case, their scene of activity is so close that it is not surprising that they are found in operation in the same person. They are both, also, probably due to some inherited or acquired idiosyncrasy in regard to the metabolism of the food.

AS might well be expected that interesting group of diseases of vaso-motor and trophic nerve origin--Acroparaesthesias, Raynaud's Disease, and Eryrmthromelalgia--supply a number of cases associated with oedema, as reported by Cassirer,(9) Schlessinger,(60) Oppenheim,(53) and others.

In Exophthalmic Goitre, another disease in which the vaso-motor system has its stability greatly upset, it has been clearly shown by Maude (45) that oedemas and gasto-intestinal crises are of not uncommon occurrence, and undoubted association with true Angioneurotic Oedema as shown in a case of Joseph's (36) and others.

In the group of the Erythemas, including Purpura, associated cases are reported by Osler.

Cases complicated with Malaria are mentioned by Matas (44) and Keefe, (37) Rheumatoid Arthritis by Jamieson, (35) and Acute Articular Rheumatism by Coutarde. (12)

D I A G N O S I S.

Properly speaking there is only one disease that can be confused with Angioneurotic Oedema the large-whealed form of Urticaria, or Giant Urticaria. For many years they were practically considered to be identical by many dermatologists, but, as the clinical conception of Angioneurotic Oedema has become more clearly defined, and especially in the last two or three years, the most of the standard text books on Skin Disease, treat the two diseases under separate sections, while of course pointing out the closeness of the alliance between them.

Between typical Angioneurotic Oedema and typical Urticaria no possible mistake in diagnosis can arise. In the former the oedematous swelling is ordinarily large, pale, free from itch, with no accompanying fever, and situated on the exposed parts of the body, and no article of diet is to be blamed for its onset.

In the latter the eruption is , as a rule, smaller, is red in part, with an intolerable itch, is attended with more or less fever, is not uncommonly on the parts of the body covered with clothing, and more often than not some special article of diet is directly responsible for the out-break.

It is important to remember that the occurrence

of Urticaria in family groups is not upon the firmly established basis as in Angioneurotic Oedema.

It must be admitted, however, that border-land cases do occur in which the diagnosis between the two forms of disease are extremely difficult, although I think a careful perusal of the reported cases will lead to the convication that such cases are by no means of such frequent occurrence as some authors have considered.

The oedemas of Hysterical patients often cause difficulty in diagnosis. In this condition, however, the oedema is mostly more extensive, often embracing the two limbs on the same side of the body; and it usually lasts much longer. Altered sensations, usually anaesthesia, are present in the affected parts, and hysterical palsies and contractures are frequent accompaniments. It is, as might be expected, by no means easy at times to draw a clear dividing line between the high strung nervous temperament which so often forms the basis for Angioneurotic Oedema, and a mild form of Hysteria, though here too the occaseon for discrimination, judging from the literature, does not arise so frequently as has been supposed.

Gross Functional Neuroses, and Organic Nervous Diseases, such as Syringomyelia, and Tabes must be ruled out of consideration by the fact that a supposition that good general health has been looked upon as one of the prominent features of Angioneurotic

Oedema. The same consideration, the non-pitting on pressure, the transient and paroxysmal character of this oedema are features which prevent confusion with oedemas arising in the course of Cardiac, Renal and many other diseases. The absence of fever differentiates it from Erysipelas.

Erythema multiforme is mostly confined to back of hand or foot, is usually symmetrical, and lasts longer.

Erythema nodosum is practically confined to the limbs, is painful on pressure, is purplish in colour, and in disappearing shows bruise-like changes in hue.

PROGNOSIS.

The question of prognosis both as regards the severity of symptoms and danger to life is, to a great extent, conditioned by whether we have to do with a pataent with a definite history of hereditary tendancy, or not. In the latter case the prognosis in regard to life is a thoroughly good one, especially if neither the tongue nor the throat are seats of the affection. In regard to cure the prognosis is by no means hopeful. The intermittent, paroxysmal, nature of the disease has become quite established. It shows great vagaries in regard to its periods of relapse, and when the oedema has for long periods disappeared at one spot it will suddenly make its reappearance at another place. Although, as a rule, the general health is not affected, yet, as so often happens, when the face is affected with disfiguring oedema, the frequent necessity of keeping to the house for several days at a time, must through the annoyance and confinement tell at length upon the general health of the patient. When the affection attacks the tongue or throat the embarrassment of the breathing has a very depressing effect.

In the family cases the prognosis becomes much more grave in regard to the severity of the effect of

the so commonly occurring gastro-intestinal attacks upon the general health. When the throat is affected the prognosis as regards life is of the gloomiest description, as has been clearly shown by the cases narrated. I may add here that in addition to the fatality of the affection of the throat in family cases, two others, occurring in solitary patients, are recorded by Mettler (46) and by Straussler (73) and Calve (8). But, apart from the consideration of longevity in the family cases, as has been so clearly pointed out by Ensor (22) in his valuable paper, other questions regarding the patient's prospects in life present themselves, namely in regard to marriage and life insurance; and the possibility of the suspicion of foul-play and the slur of suicide may find occasion to arise through the often tragically abrupt termination of life in these cases of Laryngeal Oedema. The possibility of a mistaken diagnosis leading to a surgical operation for Gastro-intestinal condition has also to be faced. Halstead (30) has also pointed out the risk that such patients may run through the oedema being induced in susceptible persons through antitoxic serum injections, and he argues that some of the fatal cases reported are due to this cause.

TREATMENT.

It may be said at the outset that no therapeutic measure has, so far, been found to have any special benefit in Angioneurotic Oedema. Its tendancy to occur in paroxysmal out-breaks which spontaneously subside and recur at more or less frequent intervals make it difficult to decide upon the special effect of the treatment adopted. Quincke,[62] in his original paper, expresses his belief as to the value of Atropine. Kreibich[40] strongly advocates the use of Arsenic as he believes that its useful effect in calming the nervous excitement in Chorea is an indication that it would bring about a more stable condition of the Vaso-motor centre. Mendel,[88] who is a supporter of the view that auto-intoxication has a great deal to do with the causation of this malady, strongly recommends the use of Aspirin on account of its antiseptic action.

Lowman,[43] on the supposition that a want of proper coagulability of the blood contributes to the oedema advocates the use of Chloride of calcium.

Forster[26] has used, he thinks, with decided benefit Ichthyol pills, which he had previously found of use in the vaso-motor disturbances of the climateric period. The use of this drug is strongly advocated

by Norman Walker[81] in the allied disease, Urticaria.

Carey[89] advises the use of Thyroid Extract, which has also proved of value in the case of Whiting, reported by me.

Truman[75] speaks in favour of Quinine, which has also proved of use in cases of Matas and Keefe associated with Malaria

Osler[57] thinks that some of his patients were improved by Nitro-glycerine.

PATHOLOGY.

The General Pathology of Angioneurotic Oedema. is obscure. It is mostly assumed, as, in the case of the allied disease, Urticaria, that it is due to an unstable condition of the vaso-motor system, but beyond that very little more can be definitely affirmed. The Physiology of the Sympathetic System, with which the vaso-motor is most intimately linked, is not yet able to give any satisfactory aid in the solution of the problem. Kreibich (40) thinks that the vaso-dilator nerves are chiefly effective in producing the oedema, which he compares to the turgescence produced by the dilator action of the Nervi errigentes, which are capable of being brought into action by peripheral or central action. Whether increased blood pressure is alone sufficient to lead to increased permeability of the capilliary wall, or whether the action of some unknown product of metabolism circulating in the blood stimulates the capillary epithelial membrane to increased secretion of lymph (according to HEIDENHAIN) or causes damage to it and so allows more easy transudation (according to Starling) it is at the present time impossible to determine. Quincke (63), who has spent a life-time in investigating this disease, writing in

1904, says "The view of an auto-intoxication from the intestines has much to be said for it; but the morbid condition is to be considered as arising not through direct irritation of the gastro-intestinal mucous membrane, but through the action of an absorbed poison on vaso-motor, or trophic nerves."

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